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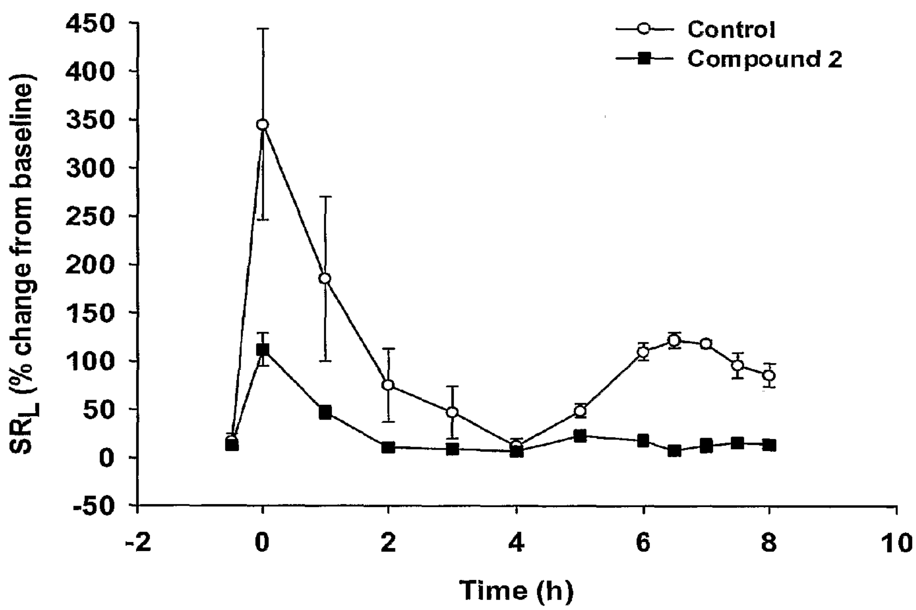
(54) Title: NOVEL PHOSPHONIC ACID COMPOUNDS AS INHIBITORS OF SERINE PROTEASES



(57) Abstract: The present invention is directed to phosphonic acid compounds useful as serine protease inhibitors, compositions thereof and methods for treating inflammatory and serine protease mediated disorders.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

NOVEL PHOSPHONIC ACID COMPOUNDS AS INHIBITORS OF SERINE PROTEASES

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims benefit of provisional application Serial Number 60/330,343, filed 19 October 2001 and US Serial No. 10/273,208 filed October 17, 2002, which are hereby incorporated by reference.

FIELD OF THE INVENTION

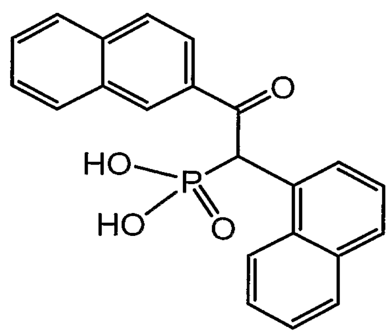
The present invention relates to certain novel compounds, methods for preparing the compounds, compositions, intermediates and derivatives thereof and for treating inflammatory and serine protease mediated disorders. More particularly, the phosphonic acid compounds of the present invention are serine protease inhibitors useful for treating inflammatory and serine protease mediated disorders.

BACKGROUND OF THE INVENTION

Serine proteases represent a broad class of endopeptidases that are involved in physiological processes such as blood coagulation, complement activation, phagocytosis and turnover of damaged cell tissue. For example, cathepsin G (cat G) is a chymotrypsin-like serine protease found in the azurophilic granules of polymorphonuclear leukocytes. Along with other serine proteases such as human neutrophil elastase and protease 3, cat G functions to degrade proteins during inflammatory responses. Cat G is thought to degrade human elastin during chronic lung inflammation, a process which may in part be responsible for asthma, pulmonary emphysema, chronic obstructive pulmonary diseases (COPD) as well as other pulmonary inflammatory conditions. Similarly, human chymase (HC) is a chymotrypsin-like serine

protease synthesized in mast cells. HC has a variety of functions, including degradation of extracellular matrix proteins, cleavage of angiotensin I to angiotensin II and activation of matrix proteases and cytokines. Inadequate control by their natural inhibitors can cause these enzymes to degrade healthy constituents of the extracellular matrix, and thereby contribute to inflammatory disorders such as asthma, emphysema, bronchitis, psoriasis, allergic rhinitis, viral rhinitis, ischemia, arthritis and reperfusion injury. Thus, small molecule inhibitors of cat G and HC are likely to represent useful therapeutic agents.

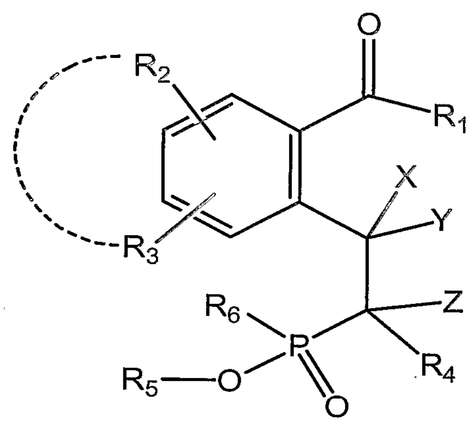
US Patent 5,508,273 to Beers, et al. and *Bioorganic & Med. Chem. Lett.*, **1995**, 5, (16), 1801-1806 describe phosphonic acid compounds useful in treating bone wasting diseases. In particular, 1-napthylmethylphosphonic acid derivatives have been described as osteoclastic acid phosphatase inhibitors of the formula:



Accordingly, it is an object of the present invention to provide phosphonic acid compounds that are serine protease inhibitors (in particular, inhibitors of cathepsin G and chymase) useful for treating inflammatory and serine protease mediated disorders. It is another object of the invention to provide a process for preparing phosphonic or phosphinic acid compounds, compositions, intermediates and derivatives thereof. It is a further object of the invention to provide methods for treating inflammatory and serine protease mediated disorders.

SUMMARY OF THE INVENTION

This invention is directed to compounds of Formula (I):



Formula (I)

wherein

R_1 is selected from the group consisting of a heterocyclyl ring (wherein the point of attachment for the heterocyclyl ring at R_1 is a nitrogen ring atom) and $-N(R_7R_8)$; wherein the heterocyclyl ring is optionally substituted with one to two substituents independently selected from the group consisting of:

a). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, heteroaryl, $(halo)_{1-3}$ and hydroxy;

b). C_{1-8} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of carboxyl, $(halo)_{1-3}$ and hydroxy;

c). aryl;

d). heteroaryl;

e). cyano;

f). halogen;

g). hydroxy;

h). nitro; and,

i). heterocyclyl optionally substituted with one to two substituents independently selected from the group consisting of oxo and aryl; and, optionally fused with the carbon of attachment to form a spiro heterocyclyl

moiety;

and, wherein the aryl portion of the a). and i). substituent , the heteroaryl portion of the a). substituent and the c). aryl and d). heteroaryl substituents are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, cycloalkyl, heterocyclyl, aryl, aryl(C_{1-4})alkyl, aryloxy, heteroaryl, heteroaryl(C_{1-4})alkyl, halogen, hydroxy, nitro, (halo)$_{1-3}$(C_{1-4})alkyl and (halo)$_{1-3}$(C_{1-4})alkoxy;

R_7 is selected from the group consisting of hydrogen, C_{1-8} alkyl and C_{2-8} alkenyl;

R_8 is selected from the group consisting of:

aa). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), (halo)$_{1-3}$ and hydroxy;

ab). cycloalkyl;

ac). cycloalkenyl; and,

ad). heterocyclyl (wherein the point of attachment at R_8 is a carbon ring atom);

wherein the ab). cycloalkyl, ac). cycloalkenyl and ad). heterocyclyl (wherein the ad). heterocyclyl contains at least one nitrogen ring atom) substituents and the cycloalkyl, heterocyclyl, aryl and heteroaryl portions of the aa). substituent are optionally substituted with one to four substituents independently selected from the group consisting of:

ba). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), (halo)$_{1-3}$ and hydroxy;

bb). C_{1-8} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of carboxyl, (halo)$_{1-3}$ and

hydroxy;

bc). carbonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, heteroaryl, heteroaryl(C_{1-8})alkyl and heteroaryl(C_{2-8})alkenyl;

bd). aryl;

be). heteroaryl;

bf). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl;

bg). cyano;

bh). halogen;

bi). hydroxy;

bj). nitro;

bk). heterocyclyl optionally substituted with one to two oxo substituents; and,

bl). sulfonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, heteroaryl, heteroaryl(C_{1-8})alkyl and heteroaryl(C_{2-8})alkenyl;

wherein the bd). aryl, be). heteroaryl and bk). heterocyclyl substituents and the aryl and heteroaryl portions of the bc). substituent are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), (halo)$_{1-3}$ and hydroxy), C_{1-4} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of (halo)$_{1-3}$), amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), halogen, hydroxy and nitro;

and, provided that the optional substituent attached to the ad). heterocyclyl nitrogen ring atom is not selected from the group consisting of bf). amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), bh). halogen, bi). hydroxy and bj).

nitro;

R_4 is selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl and heteroaryl), aryl and heteroaryl; wherein aryl and heteroaryl and the aryl and heteroaryl portions of the substituted alkyl are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cyano, halogen, hydroxy and $(halo)_{1-3}(C_{1-8})$alkyl;

R_2 and R_3 are attached to a benzene ring and independently selected from the group consisting of

ca). hydrogen;

cb). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

cc). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

cd). C_{2-4} alkenyl;

ce). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

cf). halogen; and,

cg). hydroxy;

optionally, R_2 and R_3 together form at least one ring fused to the benzene ring; thereby providing a multiple ring system; wherein the multiple ring system is selected from the group consisting of C_9-C_{14} benzo fused cycloalkyl, C_9-C_{14} benzo fused cycloalkenyl, C_9-C_{14} benzo fused aryl, benzo fused heterocyclyl and benzo fused heteroaryl; and, wherein the multiple ring system can optionally be substituted with one to four substituents

independently selected from the group consisting of

da). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

db). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

dc). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

dd). halogen;

de). hydroxy; and,

df). nitro;

R_5 is selected from the group consisting of hydrogen and C_{1-8} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy) and aryl (optionally substituted with one to four substituents independently selected from the group consisting of C_{1-8} alkyl and halogen);

R_6 is selected from the group consisting of C_{1-8} alkyl, aryl(C_{1-8})alkyl, C_{1-8} alkoxy, aryl(C_{1-8})alkoxy, C_{2-8} alkenyl, C_{2-8} alkenyloxy, aryl(C_{2-8})alkenyl, aryl(C_{2-8})alkenyloxy, aryl, aryloxy and hydroxy;

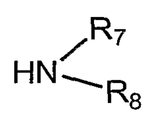
X and Y are independently selected from the group consisting of hydrogen, C_{1-8} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy), C_{1-8} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, $(halo)_{1-3}$ and

hydroxy), C_{2-8} alkenyloxy, cycloalkyl, heterocyclyl, aryl, aryloxy, heteroaryl and hydroxy; optionally, X and Y are fused together with the carbon of attachment to form a spiro cycloalkyl or heterocyclyl moiety; and, optionally, Y is not present; wherein X is one substituent attached by a double-bond selected from the group consisting of O, S, imino, (C_{1-4})alkylimino and hydroxyimino; and,

Z is selected from the group consisting of a bond, hydrogen and C_{1-8} alkyl; if Z is a bond (wherein Z forms a double bond with the carbon of attachment for X), then Y is not present and X is one substituent attached by a single-bond selected from the group consisting of hydrogen, C_{1-8} alkoxy, C_{2-8} alkenyloxy, aryloxy, aryl(C_{1-4})alkoxy and hydroxy,

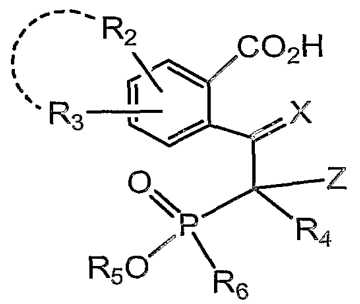
and isomers, racemates, enantiomers, diastereomers and salts thereof.

Embodiments of the present invention include a process for preparing a compound of Formula (I) comprising coupling under suitable conditions a first compound of Formula (A):

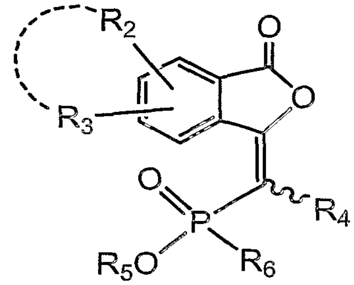


Formula (A)

with a second compound selected from the group consisting of Formula (B) and Formula (C):

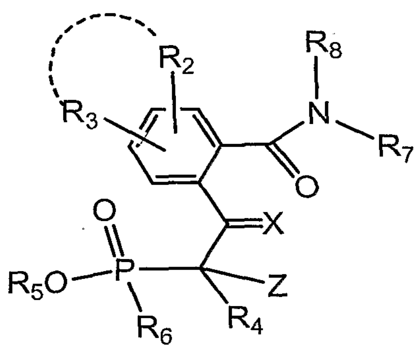


Formula (B)

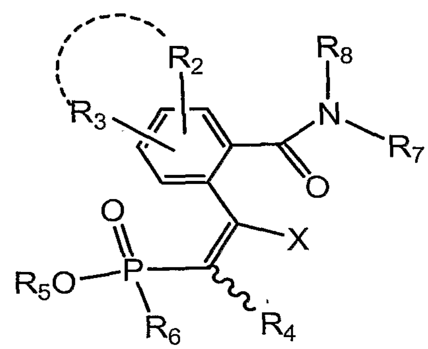


Formula (C)

to produce a third compound selected from the group consisting of Formula (D) and Formula (E):



Formula (D)



Formula (E)

wherein

R_7 is selected from the group consisting of hydrogen, $C_{1\text{-}8}$ alkyl and $C_{2\text{-}8}$ alkenyl;

R_8 is selected from the group consisting of:

aa). $C_{1\text{-}8}$ alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1\text{-}8}$ alkyl), $(\text{halo})_{1\text{-}3}$ and hydroxy;

ab). cycloalkyl;

ac). cycloalkenyl; and,

ad). heterocyclyl (wherein the point of attachment at R_8 is a carbon ring atom);

wherein the ab). cycloalkyl, ac). cycloalkenyl and ad). heterocyclyl (wherein the ad). heterocyclyl contains at least one nitrogen ring atom) substituents and the cycloalkyl, heterocyclyl, aryl and heteroaryl portions of the aa). substituent are optionally substituted with one to four substituents independently selected from the group consisting of:

ba). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy;

bb). C_{1-8} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of carboxyl, $(halo)_{1-3}$ and hydroxy;

bc). carbonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, heteroaryl, heteroaryl(C_{1-8})alkyl and heteroaryl(C_{2-8})alkenyl;

bd). aryl;

be). heteroaryl;

bf). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl;

bg). cyano;

bh). halogen;

bi). hydroxy;

bj). nitro;

bk). heterocyclyl optionally substituted with one to two oxo substituents; and,

bl). sulfonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, heteroaryl, heteroaryl(C_{1-8})alkyl and heteroaryl(C_{2-8})alkenyl;

wherein the bd). aryl, be). heteroaryl and bk). heterocyclyl substituents and the aryl and heteroaryl portions of the bc). substituent are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with

a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), (halo)$_{1-3}$ and hydroxy), C_{1-4} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of (halo)$_{1-3}$), amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), halogen, hydroxy and nitro;

and, provided that the optional substituent attached to the ad). heterocyclyl nitrogen ring atom is not selected from the group consisting of bf). amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), bh). halogen, bi). hydroxy and bj). nitro;

R_4 is selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl and heteroaryl), aryl and heteroaryl; wherein aryl and heteroaryl and the aryl and heteroaryl portions of the substituted alkyl are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cyano, halogen, hydroxy and (halo)$_{1-3}$(C_{1-8})alkyl;

R_2 and R_3 are attached to a benzene ring and independently selected from the group consisting of

ca). hydrogen;

cb). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), (halo)$_{1-3}$ and hydroxy;

cc). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of (halo)$_{1-3}$ and hydroxy;

cd). C_{2-4} alkenyl;

ce). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

cf). halogen; and,

cg). hydroxy;

optionally, R_2 and R_3 together form at least one ring fused to the benzene ring; thereby providing a multiple ring system; wherein the multiple ring system is selected from the group consisting of C_9-C_{14} benzo fused cycloalkyl, C_9-C_{14} benzo fused cycloalkenyl, C_9-C_{14} benzo fused aryl, benzo fused heterocyclyl and benzo fused heteroaryl; and, wherein the multiple ring system can optionally be substituted with one to four substituents independently selected from the group consisting of:

da). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

db). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

dc). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

dd). halogen;

de). hydroxy; and,

df). nitro;

R_5 is selected from the group consisting of hydrogen and C_{1-8} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy) and aryl (optionally substituted with one to four substituents independently selected from the group consisting of C_{1-8} alkyl and halogen);

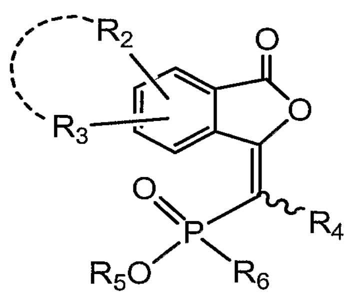
R_6 is selected from the group consisting of C_{1-8} alkyl, aryl(C_{1-8})alkyl, C_{1-8} alkoxy, aryl(C_{1-8})alkoxy, C_{2-8} alkenyl, C_{2-8} alkenyloxy, aryl(C_{2-8})alkenyl, aryl(C_{2-8})alkenyloxy, aryl, aryloxy and hydroxy;

X is selected from the group consisting of O, S, imino, (C_{1-4})alkylimino and hydroxyimino; and,

Z is selected from the group consisting of a bond, hydrogen and C_{1-8} alkyl; if Z is a bond (wherein Z forms a double bond with the carbon of attachment for X), then X is selected from the group consisting of hydrogen, C_{1-8} alkoxy, C_{2-8} alkenyloxy, aryloxy, aryl(C_{1-4})alkoxy and hydroxy,

and isomers, racemates, enantiomers, diastereomers and salts thereof.

Embodiments of the present invention include a compound of Formula (C):



Formula (C)

wherein

R_2 and R_3 are attached to a benzene ring and independently selected from the group consisting of

ca). hydrogen;

cb). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), (halo)$_{1-3}$ and hydroxy;

cc). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

cd). C_{2-4} alkenyl;

ce). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

cf). halogen; and,

cg). hydroxy;

optionally, R_2 and R_3 together form at least one ring fused to the benzene ring; thereby providing a multiple ring system; wherein the multiple ring system is selected from the group consisting of C_9-C_{14} benzo fused cycloalkyl, C_9-C_{14} benzo fused cycloalkenyl, C_9-C_{14} benzo fused aryl, benzo fused heterocyclyl and benzo fused heteroaryl; and, wherein the multiple ring system can optionally be substituted with one to four substituents independently selected from the group consisting of

da). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

db). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

dc). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

dd). halogen;

de). hydroxy; and,

df). nitro;

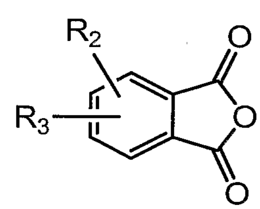
R_4 is selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl and heteroaryl), aryl and heteroaryl; wherein aryl and heteroaryl and the aryl and heteroaryl portions of the substituted alkyl are optionally substituted with one to four substituents independently selected from the

group consisting of C_{1-4} alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cyano, halogen, hydroxy and $(halo)_{1-3}(C_{1-8})$alkyl;

R_5 is selected from the group consisting of hydrogen and C_{1-8} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy) and aryl (optionally substituted with one to four substituents independently selected from the group consisting of C_{1-8} alkyl and halogen); and,

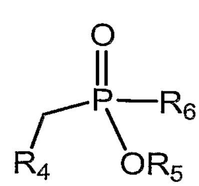
R_6 is selected from the group consisting of C_{1-8} alkyl, aryl(C_{1-8})alkyl, C_{1-8} alkoxy, aryl(C_{1-8})alkoxy, C_{2-8} alkenyl, C_{2-8} alkenyloxy, aryl(C_{2-8})alkenyl, aryl(C_{2-8})alkenyloxy, aryl, aryloxy and hydroxy.

Embodiments of the present invention include a process for making a benzolactone of Formula (C) comprising
a) reacting an anhydride of Formula (F):



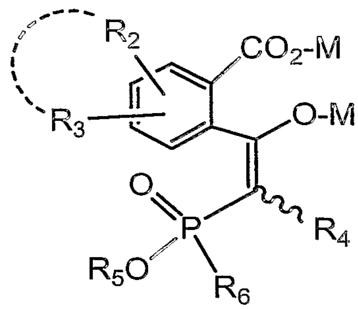
Formula (F)

with a compound of Formula (G):



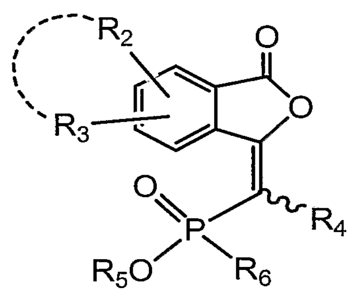
Formula (G)

under suitable conditions in the presence of an alkali metal (M) to provide a compound of Formula (H):



Formula (H)

b) and, reacting the compound of Formula (H) under conditions suitable to form the benzolactone of Formula (C):



Formula (C)

wherein

R_2 and R_3 are attached to a benzene ring and independently selected from the group consisting of

ca). hydrogen;

cb). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), (halo)$_{1-3}$ and hydroxy;

cc). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of (halo)$_{1-3}$ and hydroxy;

cd). C_{2-4} alkenyl;

ce). amino substituted with two substituents independently selected from the

group consisting of hydrogen and C_{1-4} alkyl;

cf). halogen; and,

cg). hydroxy;

optionally, R_2 and R_3 together form at least one ring fused to the benzene ring; thereby providing a multiple ring system; wherein the multiple ring system is selected from the group consisting of C_9-C_{14} benzo fused cycloalkyl, C_9-C_{14} benzo fused cycloalkenyl, C_9-C_{14} benzo fused aryl, benzo fused heterocyclyl and benzo fused heteroaryl; and, wherein the multiple ring system can optionally be substituted with one to four substituents independently selected from the group consisting of

da). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

db). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

dc). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

dd). halogen;

de). hydroxy; and,

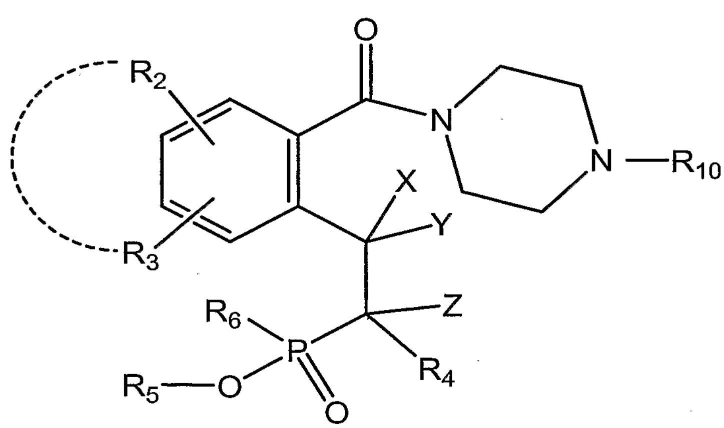
df). nitro;

R_4 is selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl and heteroaryl), aryl and heteroaryl; wherein aryl and heteroaryl and the aryl and heteroaryl portions of the substituted alkyl are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cyano, halogen, hydroxy and $(halo)_{1-3}(C_{1-8})$alkyl;

R_5 is selected from the group consisting of hydrogen and C_{1-8} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy) and aryl (optionally substituted with one to four substituents independently selected from the group consisting of C_{1-8} alkyl and halogen); and

R_6 is selected from the group consisting of C_{1-8} alkyl, aryl(C_{1-8})alkyl, C_{1-8} alkoxy, aryl(C_{1-8})alkoxy, C_{2-8} alkenyl, C_{2-8} alkenyloxy, aryl(C_{2-8})alkenyl, aryl(C_{2-8})alkenyloxy, aryl, aryloxy and hydroxy.

Embodiments of the present invention include compounds of Formula (II):



Formula (II)

wherein

R_{10} is selected from the group consisting of:

a). sulfonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, heteroaryl(C_{1-8})alkyl and heteroaryl(C_{2-8})alkenyl;

b). carbonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl,

heterocycl heteroaryl, heteroaryl(C_{1-8})alkyl, heteroaryl(C_{2-8})alkenyl, -OR_{11} and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, aryl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

c). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, (halo)$_{1-3}$, hydroxy, -C(O)R_{12} and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

d). aryl;

e). heteroaryl;

f). cycloalkyl

g). cycloalkenyl ; and,

h). heterocyclyl

wherein the heterocycl, cycloalkyl, cycloalkenyl portion of a)., b)., and c)., the cylcoalkyl f)., cylcoalkenyl g)., and heterocyclyl h). are optionally substituted with one to two substituents independently selected from the group consisting of:

ea). oxo

eb). carbonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl , aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl heteroaryl, heteroaryl(C_{1-8})alkyl, heteroaryl(C_{2-8})alkenyl and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

ec). C_{1-8} alkyl optinally substituted with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl), aryl,

cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, $(halo)_{1-3}$, and hydroxy;

ed). aryl; and

ef). $(halo)_{1-3}$

wherein the aryl portion of the a)., b)., c)., ec). and ed). substituents , the heteroaryl portion of the a)., b)., c). and ec). substituents and the d). aryl and e). heteroaryl substituents are optionally substituted with one to four substituents independently selected from the group consisting of

fa). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, $(halo)_{1-3}$, hydroxy, $-C(O)R_{12}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

fb). C_{2-4} alkenyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy;

fc). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

fd). cycloalkyl,

fe). heterocyclyl,

ff). aryl optionally substituted with one to four substituents independently selected from the group consisting of C_{1-8} alkyl and halogen;

fg). heteroaryl,

fh). hydroxy;

fi). hydroxy;

fj). nitro; and

fk). $(halo)_{1-3}$;

wherein the aryl portion of the arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl

of fa). are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy), C_{1-4} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$), amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), halogen, hydroxy and nitro.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the percent change in specific lung resistance (SR_L) from baseline for Compound **2** compared to control in a spontaneous *ascaris suum* antigen-induced model of asthma in sheep over an 8 hour period.

Figure 2 shows the change in the cumulative carbachol dose required to increase SR_L 400% (PC 400) from a baseline value (BSL) measured at 24 hours post-dosing of Compound **2** in the spontaneous *ascaris suum* antigen-induced model of asthma in sheep compared to a 24 hour post-dosing challenge with carbachol (Post Antigen).

DETAILED DESCRIPTION OF THE INVENTION

Embodiments of the present invention include those compounds wherein R_1 is selected from the group consisting of a heterocyclyl ring (wherein the point of attachment for the heterocyclyl ring at R_1 is a nitrogen ring atom) and $-N(R_7R_8)$; wherein the heterocyclyl ring is optionally substituted with a substituent selected from the group consisting of a). aryl(C_{1-4})alkyl, c). aryl, d).

heteroaryl and i). heterocyclyl (optionally substituted with one to two substituents independently selected from the group consisting of oxo and aryl; and, optionally fused with the carbon of attachment to form a spiro heterocyclyl moiety); and, wherein the aryl portion of the a). and i). substituent and the c). aryl substituent are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, halogen, hydroxy, $(halo)_{1-3}(C_{1-4})$alkyl and $(halo)_{1-3}(C_{1-4})$alkoxy; and, all other variables are as previously defined.

Preferably, R_1 is selected from the group consisting of a heterocyclyl ring (wherein the point of attachment for the heterocyclyl ring at R_1 is a nitrogen ring atom) and $-N(R_7R_8)$; wherein the heterocyclyl ring is optionally substituted with a substituent selected from the group consisting of a). aryl(C_{1-4})alkyl, c). aryl, d). heteroaryl and i). heterocyclyl (optionally substituted with two substituents independently selected from the group consisting of oxo and aryl; and, optionally fused with the carbon of attachment to form a spiro heterocyclyl moiety); and, wherein the aryl portion of the a). and i). substituent and the c). aryl substituent are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4} alkoxy and aryl; and, all other variables are as previously defined.

More preferably, R_1 is selected from the group consisting of pyrrolidinyl, piperidinyl and $-N(R_7R_8)$; wherein the point of attachment for pyrrolidinyl and piperidinyl is a nitrogen ring atom; and, wherein pyrrolidinyl and piperidinyl are optionally substituted with a substituent selected from the group consisting of a). phenylethyl, c). phenyl (optionally substituted with methoxy), d). benzothiazolyl and i). imidazolidinyl (optionally substituted with two substituents independently selected from the group consisting of oxo and phenyl; and, optionally fused with the carbon of attachment to form a spiro moiety); and, all other variables are as previously defined.

Most preferably, R_1 is selected from the group consisting of pyrrolidinyl, piperidinyl and -N(R_7R_8); wherein the point of attachment for pyrrolidinyl and piperidinyl is a nitrogen ring atom in the one position; and, wherein pyrrolidinyl and piperidinyl are optionally substituted with a substituent selected from the group consisting of a). phenylethyl, c). phenyl (optionally substituted with methoxy), d). benzothiazolyl and i). imidazolidinyl (optionally substituted with two substituents independently selected from the group consisting of oxo and phenyl; and, optionally fused with the carbon of attachment to form a spiro moiety); and, all other variables are as previously defined.

Preferred embodiments of the present invention include those compounds wherein R_7 is selected from the group consisting of hydrogen, C_{1-4} alkyl and C_{2-4} alkenyl.

More preferably, R_7 is selected from the group consisting of hydrogen and C_{1-4} alkyl.

Most preferably, R_7 is selected from the group consisting of hydrogen and methyl.

Embodiments of the present invention include those compounds wherein R_8 is selected from the group consisting of:

aa). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of cycloalkyl, heterocyclyl, $(halo)_{1-3}$ and hydroxy;

ab). cycloalkyl;

ac). cycloalkenyl; and,

ad). heterocyclyl (wherein the point of attachment at R_8 is a carbon ring atom);

wherein the ab). cycloalkyl, ac). cycloalkenyl and ad). heterocyclyl substituents (wherein the ad). heterocyclyl contains at least one nitrogen ring atom) and the cycloalkyl portion of the aa). substituent are optionally substituted with

one to four substituents independently selected from the group consisting of:

ba). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy;

bb). C_{1-8} alkoxy;

bc). carbonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, heteroaryl, heteroaryl(C_{1-8})alkyl and heteroaryl(C_{2-8})alkenyl;

bd). aryl;

be). heteroaryl;

bf). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl;

bh). halogen;

bi). hydroxy;

bk). heterocyclyl; and,

bl). sulfonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, heteroaryl, heteroaryl(C_{1-8})alkyl and heteroaryl(C_{2-8})alkenyl;

wherein the bd). aryl, be). heteroaryl and bk). heterocyclyl substituents and the aryl and heteroaryl portions of the bc). substituent are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$), C_{1-4} alkoxy, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), halogen and hydroxy;

and, provided that the optional substituent attached to the ad). heterocyclyl nitrogen ring atom is not selected from the group consisting of bf). amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), bh). halogen, bi). hydroxy and bj).

nitro.

Preferably, R_8 is selected from the group consisting of aa). cycloalkyl(C_{1-4})alkyl, ab). cycloalkyl, ac). cycloalkenyl and ad). heterocyclyl (wherein the point of attachment for the ad). heterocyclyl at R_8 is a carbon ring atom; and, the ad). heterocyclyl contains a single nitrogen ring atom); wherein the ab). cycloalkyl, ac). cycloalkenyl and ad). heterocyclyl substituents and the cycloalkyl portion of the aa). substituent are optionally substituted with one to two substituents independently selected from the group consisting of ba). C_{1-4} alkyl, bc). carbonyl (substituted with a substituent selected from the group consisting of C_{1-4} alkyl, aryl, aryl(C_{1-4})alkyl and aryl(C_{2-4})alkenyl) and bd). aryl; wherein the bd). aryl substituent and the aryl portions of the bc). substituent are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, di(C_{1-4} alkyl)amino, halogen, hydroxy and (halo)$_{1-3}$(C_{1-4})alkyl.

More preferably, R_8 is selected from the group consisting of aa). adamant-1-ylmethyl, ab). cyclopentyl, ab). cyclohexyl, ac). cyclohexenyl, ad). pyrrolidinyl and ad). piperidinyl (wherein the point of attachment for pyrrolidinyl and piperidinyl at R_8 is a carbon ring atom); wherein ab). cyclohexyl, ac). cyclohexenyl, ad). pyrrolidinyl and ad). piperidinyl are optionally substituted with one to two substituents independently selected from the group consisting of ba). C_{1-4} alkyl, bc). carbonyl (substituted with a substituent selected from the group consisting of C_{1-4} alkyl, aryl, aryl(C_{1-4})alkyl and aryl(C_{2-4})alkenyl) and bd). aryl; wherein the bd). aryl substituent and the aryl portions of the bc). substituent are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, di(C_{1-4} alkyl)amino, halogen, hydroxy and (halo)$_{1-3}$(C_{1-4})alkyl.

Most preferably, R_8 is selected from the group consisting of aa). adamant-1-ylmethyl, ab). cyclopentyl, ab). cyclohexyl, ac). cyclohexenyl, ad).

pyrrolidinyl and ad). piperidinyl (wherein the point of attachment for pyrrolidinyl and piperidinyl at R_8 is a carbon ring atom); wherein ab). cyclohexyl, ac). cyclohexenyl, ad). pyrrolidinyl and ad). piperidinyl are optionally substituted with one to two substituents independently selected from the group consisting of ba). methyl, ba). *t*-butyl, bc). methylcarbonyl, bc). *i*-propylcarbonyl, bc). phenylcarbonyl, bc). naphthalenylcarbonyl, bc). phenethylcarbonyl, bc). phenethenylcarbonyl and bd). phenyl; and, wherein the bd). phenyl substituent and the phenyl and naphthalenyl portions of the bc). substituent are optionally substituted with one to two substituents independently selected from the group consisting of methyl, methoxy, *N,N*-dimethylamino, fluorine, bromine, hydroxy and trifluoromethyl.

Embodiments of the present invention include those compounds wherein R_2 and R_3 are attached to the benzene ring (shown in Formula I) on adjacent carbon atoms. Preferred embodiments of the present invention include those compounds wherein R_2 and R_3 are independently selected from the group consisting of ca). hydrogen, cb). C_{1-4} alkyl, cc). C_{1-4} alkoxy, cd). C_{2-4} alkenyl, ce). amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cf). halogen and cg). hydroxy; optionally R_2 and R_3 together form at least one ring fused to the benzene ring; thereby providing a multiple ring system; wherein the multiple ring system is selected from the group consisting of naphthalene and anthracene; and, wherein the multiple ring system can optionally be substituted with one to four substituents independently selected from the group consisting of da). C_{1-4} alkyl, db). C_{1-4} alkoxy, dc). amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), dd). halogen and de). hydroxy.

More preferably, R_2 and R_3 are attached to the benzene ring on adjacent carbon atoms and independently selected from the group consisting of ca). hydrogen, cb). C_{1-4} alkyl, cd). C_{2-4} alkenyl, cf). halogen and cg). hydroxy;

optionally, R_2 and R_3 together form at least one ring fused to the benzene ring; thereby providing a multiple ring system; wherein the multiple ring system is naphthalene; and, wherein the multiple ring system can optionally be substituted with one to four substituents independently selected from the group consisting of da). C_{1-4} alkyl, db). C_{1-4} alkoxy, dc). amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), dd). halogen and de). hydroxy.

Most preferably, the multiple ring system is a non-substituted naphthalene.

Embodiments of the present invention include those compounds wherein R_4 is selected from the group consisting of aryl and heteroaryl optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4} alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cyano, halogen, hydroxy and $(halo)_{1-3}(C_{1-8})$alkyl.

Preferably, R_4 is selected from the group consisting of aryl and heteroaryl (wherein heteroaryl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4} alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cyano, halogen, hydroxy and $(halo)_{1-3}(C_{1-8})$alkyl).

More preferably, R_4 is selected from the group consisting of phenyl, naphthalenyl and benzothienyl (wherein benzothienyl is optionally substituted with one to two halogen substituents).

Most preferably, R_4 is selected from the group consisting of phenyl, naphthalenyl and benzothienyl (wherein benzothienyl is optionally substituted

with a chloro substituent).

Embodiments of the present invention include those compounds wherein R_5 is selected from the group consisting of hydrogen and C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy).

Preferably, R_5 is selected from the group consisting of hydrogen and C_{1-4} alkyl.

More preferably, R_5 is selected from the group consisting of hydrogen and methyl.

Most preferably, R_5 is hydrogen.

Preferred embodiments of the present invention include those compounds wherein R_6 is selected from the group consisting of C_{1-4} alkyl, aryl(C_{1-4})alkyl, C_{1-4} alkoxy, aryl(C_{1-4})alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyloxy, aryl(C_{2-4})alkenyl, aryl(C_{2-4})alkenyloxy, aryl, aryloxy and hydroxy.

More preferably, R_6 is selected from the group consisting of methyl, methoxy, phenyloxy and hydroxy.

Most preferably, R_6 is selected from the group consisting of methyl and hydroxy.

Preferred embodiments of the present invention include those compounds wherein Y is not present and X is one substituent attached by a double-bond selected from the group consisting of O, S, imino, (C_{1-4})alkylimino

and hydroxyimino.

More preferably, Y is not present and X is one substituent attached by a double-bond selected from the group consisting of O, imino and hydroxyimino.

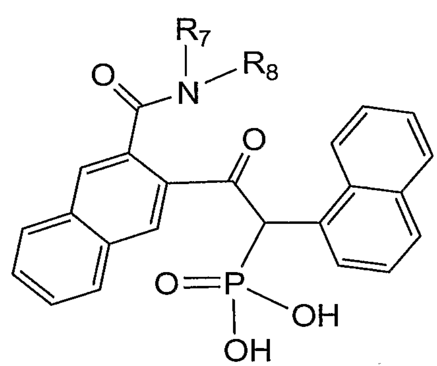
Most preferably, Y is not present and X is O attached by a double-bond.

Preferred embodiments of the present invention include those compounds wherein Z is selected from the group consisting of hydrogen and C_{1-4} alkyl.

More preferably, Z is hydrogen.

Embodiments of the present invention include those compounds of Formula (Ia) shown in Table 1.

Table 1



Formula (Ia)

wherein

R_5, R_7 and R_8 are dependently selected from the group consisting of:

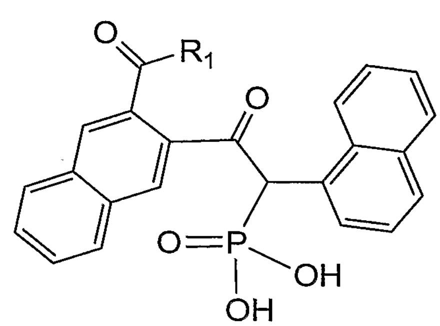
Cpd	R_7	R_8
1	CH_3	4-phenylcyclohexyl
2	CH_3	1-(2-naphthalenylcarbonyl)-4-piperidinyl
3	CH_3	1-[(6-methoxy-2-naphthalenyl)carbonyl]-3-pyrrolidinyl
4	CH_3	1-[(6-bromo-2-naphthalenyl)carbonyl]-4-piperidinyl
5	CH_3	1-[3-(4-fluorophenyl)-1-oxo-2-propenyl]-3-pyrrolidinyl

Cpd	R_7	R_8
6	CH_3	1-[1-oxo-3-phenyl-2-propenyl]-4-piperidinyl
9	CH_3	1-[3-(4-methylphenyl)-1-oxo-2-propenyl]-4-piperidinyl
10	CH_3	1-[1-oxo-3-[4-(trifluoromethyl)phenyl]-2-propenyl]-4-piperidinyl
13	CH_3	1-[3-[4-(dimethylamino)phenyl]-1-oxo-2-propenyl]-4-piperidinyl
15	CH_3	1-benzoyl-4-piperidinyl
17	CH_3	Cyclohexyl
18	CH_3	1-[1-oxo-3-[4-(trifluoromethyl)phenyl]propyl]-4-piperidinyl
20	CH_3	1-(2-methyl-1-oxopropyl)-4-piperidinyl
21	CH_3	Cyclopentyl
22	CH_3	4-(1,1-dimethylethyl)cyclohexyl
24	CH_3	1-[(6-hydroxy-2-naphthalenyl)carbonyl]-4-piperidinyl
26	CH_3	1-acetyl-4-piperidinyl
27	CH_3	4-methylcyclohexyl
28	CH_3	adamant-1-ylmethyl
29	CH_3	4-phenyl-3-cyclohexen-1-yl
And,		
30	H	1-(2-naphthalenylcarbonyl)-4-piperidinyl

and racemates, enantiomers, diastereomers and salts thereof.

Embodiments of the present invention include those compounds of Formula (Ib) shown in Table 2.

Table 2



Formula (Ib)

wherein

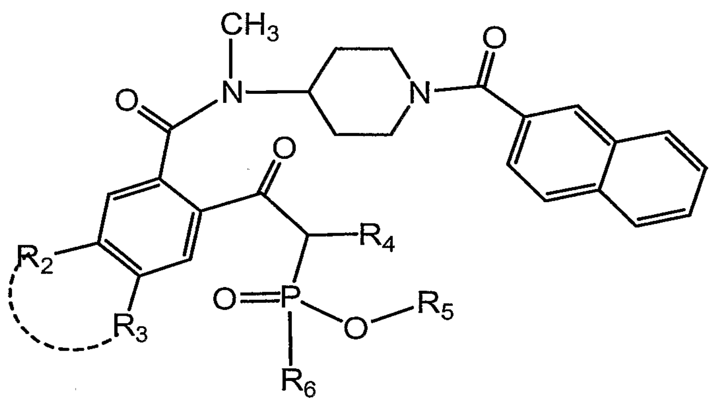
R_1 is selected from the group consisting of:

Cpd	R_1
7	4-phenyl-1-piperidinyl
8	4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl
12	4-(4-methoxyphenyl)-1-piperidinyl
14	4-(3-methoxyphenyl)-1-piperidinyl
16	4-(2-benzothiazolyl)-1-piperidinyl
19	3-phenyl-1-pyrrolidinyl
and,	
25	3-(2-phenylethyl)-1-pyrrolidinyl

and racemates, enantiomers, diastereomers and salts thereof.

Embodiments of the present invention include those compounds of Formula (Ic) shown in Table 3.

Table 3



Formula (Ic)

wherein R_2, R_3, R_4, R_5 and R_6 are dependently selected from the group consisting of:

Cpd	R_2	R_3	R_4	R_5	R_6
11	taken together to form phenyl		phenyl	H	OH
23	taken together to form phenyl		1-naphthalenyl	CH_3	OH
31	H	H	1-naphthalenyl	H	OH
32	taken together to form phenyl		1-naphthalenyl	H	CH_3

And,

Cpd	R_2	R_3	R_4	R_5	R_6
33	taken together to form phenyl		5-chloro-benzo[*b*]thien-3-yl	H	OH

and racemates, enantiomers, diastereomers and salts thereof.

In embodiments for Formula (II) the preferred embodiments of R_2, R_3, R_4, R_5 and R_6 are as previously described.

Preferably, R_{10} is selected from the group consisting of

a). sulfonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, heteroaryl(C_{1-8})alkyl and heteroaryl(C_{2-8})alkenyl;

b). carbonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl heteroaryl, heteroaryl(C_{1-8})alkyl, heteroaryl(C_{2-8})alkenyl, $-OR_{11}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, aryl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

c). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, $(halo)_{1-3}$, hydroxy, $-C(O)R_{12}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

d). aryl; and

e). heteroaryl;

wherein the heterocycl, cycloalkyl, cycloalkenyl portion of a)., b)., and c). are optionally substituted with one to two substituents independently selected from the group consisting of:

ea). oxo

eb). carbonyl substituted with a substituent selected from the group

consisting of C_{1-8} alkyl , aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl heteroaryl, heteroaryl(C_{1-8})alkyl, heteroaryl(C_{2-8})alkenyl and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

ec). C_{1-8} alkyl optinally substituted with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl), aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, (halo)$_{1-3}$, and hydroxy;

ed). aryl; and

ef). (halo)$_{1-3}$

wherein the aryl portion of the a)., b)., c)., ec). and ed). substituents , the heteroaryl portion of the a)., b)., c). and ec). substituents and the d). aryl and e). heteroaryl substituents are optionally substituted with one to four substituents independently selected from the group consisting of

fa). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, (halo)$_{1-3}$, hydroxy, -C(O)R_{12} and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

fb). C_{2-4} alkenyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), (halo)$_{1-3}$ and hydroxy;

fc). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of (halo)$_{1-3}$ and hydroxy;

fd). cycloalkyl,

fe). heterocyclyl,

ff). aryl optionally substituted with one to four substituents independently

selected from the group consisting of C_{1-8} alkyl and halogen;

fg). heteroaryl,

fh). hydroxy;

fi). hydroxy;

fj). nitro; and

fk). $(halo)_{1-3}$;

wherein the aryl portion of the arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl of fa). are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy), C_{1-4} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$), amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), halogen, hydroxy and nitro.

Preferably, R_{11} is selected from the group consisting of :

aa). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl portions of the aa). substituent are optionally substituted with one to four substituents independently selected from the group consisting of:

ba). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

bb). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a

substituent selected from the group consisting of carboxyl, $(halo)_{1-3}$ and hydroxy;

bc). carbonyl substituted with a substituent selected from the group consisting of C_{1-4} alkyl, aryl, aryl(C_{1-4})alkyl, aryl(C_{2-4})alkenyl, heteroaryl, heteroaryl(C_{1-4})alkyl and heteroaryl(C_{2-4})alkenyl;

bd). aryl;

be). heteroaryl;

bf). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

bh). $(halo)_{1-3}$;

bi). hydroxy; and

bk). heterocyclyl optionally substituted with one to two oxo substituents; and,

wherein the bd). aryl, be). heteroaryl and bk). heterocyclyl substituents and the aryl and heteroaryl portions of the bc). substituent are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy), C_{1-4} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$), amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), halogen, hydroxy and nitro;

Preferably , R_{12} is selected from the group consisting of C_{1-4} alkyl, aryl, aryl(C_{1-4})alkyl, aryl(C_{2-4})alkenyl, cycloalkyl, cycloalkenyl, heterocycl heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryl(C_{2-4})alkenyl, $-OR_{11}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-4} alkyl, arylC_{1-4} alkyl, arylcarbonyl, arylC_{1-4} alkyl carbonyl and heteroaryl C_{1-4} alkyl); wherein the aryl, the heteroaryl portion of R_{12} are optionally substituted with one to four substituents independently selected from the group consisting

of:

fa). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, $(halo)_{1-3}$, hydroxy, $-C(O)R_{11}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-4} alkyl, arylcarbonyl, arylC_{1-4} alkyl carbonyl and heteroaryl C_{1-4} alkyl);

fb). C_{2-4} alkenyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

fc). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

fd). cycloalkyl,

fe). heterocyclyl,

ff). aryl optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl and halogen;

fg). heteroaryl,

fh). $(halo)_{1-3}$;

fi). hydroxy; and

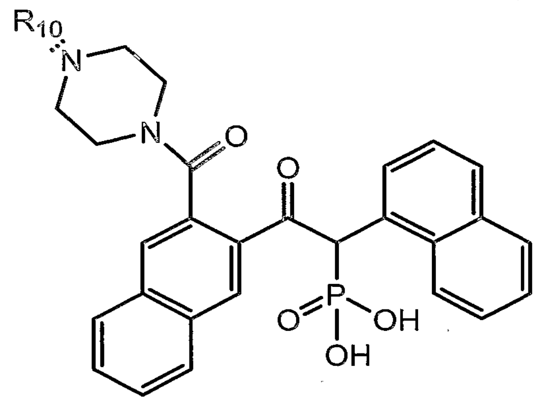
fj). nitro;

wherein the aryl portion of the arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl of fa). are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy), C_{1-4} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$), amino (substituted with two substituents independently selected from the group consisting of hydrogen

and C_{1-4} alkyl), halogen, hydroxy and nitro;

Embodiments of the present invention include those compounds of Formula (IIa) shown in Table 4.

Table 4



Cpd	R_{10}
37	naphthalene-2-yl-acetyl
38	2-naphthoyl
39	1-(4-hydroxyphenyl)
40	1-(4-methoxyphenyl)
41	N-[5-(sulfonyl)-thiophene-2-ylmethyl]-benzamide
42	6-chloro-5-sulfonyl-imidazo[2,1-b]thiazole
43	Naphthyl-2-aminocarbonyl
44	1-(4-fluorophenyl)

and racemates, enantiomers, diastereomers and salts thereof.

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic “pharmaceutically acceptable salts.” FDA approved pharmaceutically acceptable salt forms (*Ref. International J. Pharm.* **1986**, 33, 201-217; *J. Pharm. Sci.*, **1977**, Jan, 66(1), p1) include pharmaceutically acceptable acidic/anionic or basic/cationic salts.

Pharmaceutically acceptable acidic/anionic salts include, and are not

limited to acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphospate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate and triethiodide. Organic or inorganic acids also include, and are not limited to, hydriodic, perchloric, sulfuric, phosphoric, propionic, glycolic, methanesulfonic, hydroxyethanesulfonic, oxalic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, saccharinic or trifluoroacetic acid.

Pharmaceutically acceptable basic/cationic salts include, and are not limited to aluminum, 2-amino-2-hydroxymethyl-propane-1,3-diol (also known as tris(hydroxymethyl)aminomethane, tromethane or "TRIS"), ammonia, benzathine, *t*-butylamine, calcium, calcium gluconate, calcium hydroxide, chloroprocaine, choline, choline bicarbonate, choline chloride, cyclohexylamine, diethanolamine, ethylenediamine, lithium, LiOMe, L-lysine, magnesium, meglumine, NH_3, NH_4OH, N-methyl-D-glucamine, piperidine, potassium, potassium-*t*-butoxide, potassium hydroxide (aqueous), procaine, quinine, SEH, sodium, sodium carbonate, sodium-2-ethylhexanoate, sodium hydroxide, triethanolamine (TEA) or zinc.

Compounds of the present invention may be contacted with a pharmaceutically acceptable cation selected from the group consisting of aluminum, 2-amino-2-hydroxymethyl-propane-1,3-diol (also known as tris(hydroxymethyl)aminomethane, tromethane or "TRIS"), ammonia, benzathine, *t*-butylamine, calcium, calcium gluconate, calcium hydroxide, chloroprocaine, choline, choline bicarbonate, choline chloride, cyclohexylamine,

diethanolamine, ethylenediamine, lithium, LiOMe, L-lysine, magnesium, meglumine, NH_3, NH_4OH, N-methyl-D-glucamine, piperidine, potassium, potassium-*t*-butoxide, potassium hydroxide (aqueous), procaine, quinine, SEH, sodium, sodium carbonate, sodium-2-ethylhexanoate, sodium hydroxide, triethanolamine (TEA) and zinc to form a salt.

Preferred cations for use with the instant compounds are selected from the group consisting of benzathine, *t*-butylamine, calcium gluconate, calcium hydroxide, choline bicarbonate, choline chloride, cyclohexylamine, diethanolamine, ethylenediamine, LiOMe, L-lysine, NH_3, NH_4OH, N-methyl-D-glucamine, piperidine, potassium-*t*-butoxide, potassium hydroxide (aqueous), procaine, quinine, sodium carbonate, sodium-2-ethylhexanoate, sodium hydroxide, triethanolamine and tromethane.

More preferably, cations for use with the instant compounds are selected from the group consisting of *t*-butylamine, NH_4OH and tromethane.

Most preferably, the cation for use with the instant compounds is tromethane.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds, which are readily convertible *in vivo* into an active compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or a prodrug compound which would be obviously included within the scope of the invention although not specifically disclosed including, but not limited to diphenylphosphonate or diphenylphosphinate esters of certain of the instant compounds. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier,

1985. Phosphonic acid prodrugs (as described in De Lombaert S., et al, Non-Peptidic Inhibitors of Neutral Endopeptidase 24.11; Design and Pharmacology of Orally Active Phosphonate Prodrugs, *Bioorganic and Medicinal Chemistry Letters,* **1995**, 5(2), 151-154; and, De Lombaert S., et al, *N*-Phosphonomethyl Dipeptides and Their Phosphonate Prodrugs, a New Generatrion Neutral Endopeptidase (NEP, EC 3.424.11) Inhibitors, *J. Med. Chem.,* **1994**, 37, 498-511) and phosphinic acid prodrugs are intended to be included within the scope of the present invention.

The compounds according to this invention may have at least one chiral center and thus may exist as enantiomers. In addition, the compounds of the present invention may also possess two or more chiral centers and thus may also exist as diastereomers. Where the processes for the preparation of the present compounds give rise to a mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. Accordingly, the compounds may be prepared as a racemic mixture or, by either enantiospecific synthesis or resolution, as individual enantiomers. The compounds may, for example, be resolved from a racemic mixture into their component racemates by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active base, followed by fractional crystallization and regeneration of the compounds of this invention. The racemic mixture may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The compounds according to this invention wherein Z forms a double bond with the carbon of attachment for X, Y is not present and X is hydroxy may have at least one keto-enol tautomeric form and thus may exist in equilibirum as geometric isomers. It is to be understood that all such isomers

and mixtures thereof are encompassed within the scope of the present invention.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

As used herein, unless otherwise noted, “alkyl” whether used alone or as part of a substituent group refers to straight and branched carbon chains having 1 to 8 carbon atoms or any number within this range. The term "alkoxy" refers to an -O-alkyl substituent group, wherein alkyl is as defined supra. Similarly, the terms “alkenyl” and “alkynyl” refer to straight and branched carbon chains having 2 to 8 carbon atoms or any number within this range, wherein an alkenyl chain has at least one double bond in the chain and an alkynyl chain has at least one triple bond in the chain. An alkyl and alkoxy chain may be substituted on a terminal carbon atom or, when acting as a linking group, within the carbon chain.

The term “cycloalkyl” refers to saturated, moncyclic or polycyclic hydrocarbon rings of from 3 to 20 carbon atom members (preferably from 3 to 12

carbon atom members). Further, a cycloalkyl ring may optionally be fused to one or more cycloalkyl rings. Examples of such rings include, and are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or adamantyl.

The term “cycloalkenyl” refers to partially unsaturated, nonaromatic moncyclic or polycyclic hydrocarbon rings of 3 to 20 carbon atom members (preferably from 3 to 12 carbon atom members). Typically, a 3 to 5 member ring contains one double bond and a 6 to 9 member ring contains multiple double bonds. Further, a cycloalkenyl ring may optionally be fused to one or more cycloalkyl rings or cycloalkenyl rings. Examples of such rings include, and are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl.

The term “heterocyclyl” refers to a nonaromatic cyclic ring of 5 to 8 members in which 1 to 4 members are nitrogen or a nonaromatic cyclic ring of 5 to 8 members in which zero, one or two members are nitrogen and one member is oxygen or sulfur; wherein, optionally, the ring contains zero, one or two unsaturated bonds. Alternatively, the heterocyclyl ring may be fused to a benzene ring (benzo fused heterocyclyl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen), a 5 to 7 membered cycloalkyl or cycloalkenyl ring, a 5 to 7 membered heterocyclyl ring (of the same definition as above but absent the option of a further fused ring) or fused with the carbon of attachment of a cycloalkyl, cycloalkenyl or heterocyclyl ring to form a spiro moiety. For instant compounds of the invention, the carbon atom ring members that form the heterocyclyl ring are fully saturated. Other compounds of the invention may have a partially saturated heterocyclyl ring. Additionally, the heterocyclyl can be bridged to form bicyclic rings. Preferred partially saturated heterocyclyl rings may have from one to two double bonds. Such compounds are not considered to be fully aromatic and are not referred to as heteroaryl compounds. Examples of heterocyclyl groups include, and are not limited to, pyrrolinyl (including 2*H*-pyrrole, 2-pyrrolinyl or 3-pyrrolinyl), pyrrolidinyl,

2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl. In the present invention, when R_1 is selected from heterocyclyl, the term "heterocyclyl" refers to a nonaromatic cyclic ring of 5 to 8 members in which 1 to 4 members are nitrogen; wherein, the point of attachment for the heterocyclyl ring at R_1 is a nitrogen ring member; and, wherein optionally the ring contains zero, one (for 5 and 6 member rings) or two (for 6, 7 and 8 member rings) unsaturated bonds.

The term "aryl" refers to an unsaturated, aromatic monocyclic ring of 6 carbon members or to an unsaturated, aromatic polycyclic ring of from 10 to 20 carbon members. Further, an aryl ring may optionally be fused to one or more benzene rings (benzo fused aryl), cycloalkyl rings (e.g. benzo fused cycloalkyl) or cycloalkenyl rings (e.g. benzo fused cycloalkenyl) wherein, for the purpose of these definitions, the cycloalkyl rings and cycloalkenyl rings may be fused to an additional benzene ring (to provide fused multiple ring systems such as fluorene). Examples of such aryl rings include, and are not limited to, phenyl, naphthalenyl, fluorenyl, indenyl or anthracenyl.

The term "heteroaryl" refers to an aromatic ring of 5 or 6 members wherein the ring consists of carbon atoms and has at least one heteroatom member. Suitable heteroatoms include nitrogen, oxygen or sulfur. In the case of 5 membered rings, the heteroaryl ring contains one member of nitrogen, oxygen or sulfur and, in addition, may contain up to two additional nitrogens. In the case of 6 membered rings, the heteroaryl ring may contain from one to three nitrogen atoms. For the case wherein the 6 member ring has three nitrogens, at most two nitrogen atoms are adjacent. Optionally, the heteroaryl ring is fused to a benzene ring (benzo fused heteroaryl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen), a 5 to 7 membered alicyclic ring or a 5 to 7 membered heterocyclo ring (as defined supra but absent the option of a further fused ring). Examples of heteroaryl groups include, and are not limited to, furyl, thienyl, pyrrolyl, oxazolyl,

thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl; fused heteroaryl groups include indolyl, isoindolyl, indolinyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, benzothiadiazolyl, benzotriazolyl, quinolizinyl, quinolinyl, isoquinolinyl or quinazolinyl.

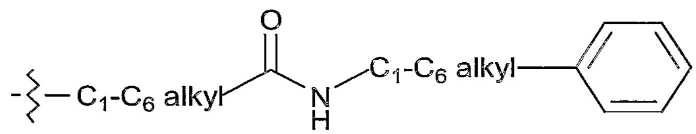
The term “arylalkyl” means an alkyl group substituted with an aryl group (e.g., benzyl, phenethyl). Similarly, the term “arylalkoxy” indicates an alkoxy group substituted with an aryl group (e.g., benzyloxy).

As used herein, the term "carboxyl " refers to the linking group -C(O)O- or (when used accordingly) to the substituent -COOH; the term “imino” refers to the substituent HN=.

Whenever the term “alkyl” or “aryl” or either of their prefix roots appear in a name of a substituent (*e.g.*, arylalkyl, alkylamino) it shall be interpreted as including those limitations given above for “alkyl” and “aryl.” Designated numbers of carbon atoms (e.g., C_1-C_6) shall refer independently to the number of carbon atoms in an alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root. However, for clarity in the terms “C_9-C_{14} benzo fused cycloalkyl”, “C_9-C_{14} benzo fused cycloalkenyl”, “C_9-C_{14} benzo fused aryl”; C_9-C_{14} refers to the number of carbon atoms both in the benzene ring (6) and the number of atoms in the ring fused to the benzene ring, but does not include carbon atoms that may be pendent from these multiple ring systems. The amount of substituents attached to a moiety “optionally substituted with one to five substituents” is limited to that amount of open valences on the moiety available for substitution.

In general, under standard nomenclature rules used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. Thus, for

example, a “phenylC_1-C_6 alkylamidoC_1-C_6alkyl” substituent refers to a group of the formula:



It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

Illustrative of the invention is a composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. Also illustrative of the invention is a composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. A further illustration of the invention is a process for making a composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier. The present invention also provides compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier.

The compounds of the present invention are useful serine protease inhibitors (in particular, inhibitors of cathepsin G and chymase) useful for treating inflammatory and serine protease mediated disorders. Some of these disorders include, inflammatory and serine protease mediated disorders include, and are not limited to, pulmonary inflammatory conditions, chronic obstructive pulmonary diseases, asthma, pulmonary emphysema, bronchitis, psoriasis, allergic rhinitis, viral rhinitis, ischemia, arthritis, glomerulonephritis, postoperative adhesion formation and reperfusion injury. These compounds would be useful in treating

disease states caused by angiotensin II including but not limited to hypertension, hypercardia myocardial infarction, arteriosclerosis, diabetic and non-diabetic retinopathy, vascular restenosis and the like. Additionally, these compounds can be used for immune modulation. The utility of the compounds to treat inflammatory and serine protease mediated disorders can be determined according to the procedures described herein.

An embodiment of the invention is a method for treating inflammatory and serine protease mediated disorders in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of any of the compounds or compositions described above. Also included in the invention is the use of a compound of Formula (I) for the preparation of a medicament for treating an inflammatory or serine protease mediated disorder in a subject in need thereof. The term "treating" as used herein refers to a method for improving, halting, retarding or palliating an inflammatory or serine protease mediated disorder in the subject in need thereof. All such methods of treatment are intended to be within the scope of the present invention.

In accordance with the methods of the present invention, the individual components of the compositions described herein can also be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

The term "subject" as used herein, refers to an animal (preferably, a mammal; most preferably, a human) who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or

medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

To prepare the compositions of this invention, one or more compounds of Formula (I) or salt thereof as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration (e.g. oral or parenteral). Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers may be found in <u>The Handbook of Pharmaceutical Excipients</u>, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

Methods of formulating compositions have been described in numerous publications such as <u>Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded</u>, Volumes 1-3, edited by Lieberman et al; <u>Pharmaceutical Dosage Forms: Parenteral Medications</u>, Volumes 1-2, edited by Avis et al; and <u>Pharmaceutical Dosage Forms: Disperse Systems</u>, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc.

In preparing a composition of the present invention in liquid dosage form for oral, topical, inhalation/insufflation and parenteral administration, any of the usual pharmaceutical media or excipients may be employed. Thus, for liquid dosage forms, such as suspensions (i.e. colloids, emulsions and dispersions)

and solutions, suitable carriers and additives include but are not limited to pharmaceutically acceptable wetting agents, dispersants, flocculation agents, thickeners, pH control agents (i.e. buffers), osmotic agents, coloring agents, flavors, fragrances, preservatives (i.e. to control microbial growth, etc.) and a liquid vehicle may be employed. Not all of the components listed above will be required for each liquid dosage form.

In solid oral preparations such as, for example, powders, granules, capsules, caplets, gelcaps, pills and tablets (each including immediate release, timed release and sustained release formulations), suitable carriers and additives include but are not limited to diluents, granulating agents, lubricants, binders, glidants, disintegrating agents and the like. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated, gelatin coated, film coated or enteric coated by standard techniques.

Preferably these compositions are in unit dosage forms from such as tablets, pills, capsules, powders, granules, lozenges, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories for administration by oral, intranasal, sublingual, intraocular, transdermal, parenteral, rectal, vaginal, inhalation or insufflation means. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tabletting ingredients such as diluents, binders, adhesives, disintegrants, lubricants, antiadherents and glidants. Suitable diluents include, but are not limited to,

starch (i.e. corn, wheat, or potato starch, which may be hydrolized), lactose (granulated, spray dried or anhydrous), sucrose, sucrose-based diluents (confectioner's sugar; sucrose plus about 7 to 10 weight percent invert sugar; sucrose plus about 3 weight percent modified dextrins; sucrose plus invert sugar, about 4 weight percent invert sugar, about 0.1 to 0.2 weight percent cornstarch and magnesium stearate), dextrose, inositol, mannitol, sorbitol, microcrystalline cellulose (i.e. AVICEL ™ microcrystalline cellulose available from FMC Corp.), dicalcium phosphate, calcium sulfate dihydrate, calcium lactate trihydrate and the like. Suitable binders and adhesives include, but are not limited to accacia gum, guar gum, tragacanth gum, sucrose, gelatin, glucose, starch, and cellulosics (i.e. methylcellulose, sodium carboxymethycellulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, and the like), water soluble or dispersible binders (i.e. alginic acid and salts thereof, magnesium aluminum silicate, hydroxyethylcellulose [i.e. TYLOSE ™ available from Hoechst Celanese], polyethylene glycol, polysaccharide acids, bentonites, polyvinylpyrrolidone, polymethacrylates and pregelatinized starch) and the like. Suitable disintegrants include, but are not limited to, starches (corn, potato, etc.), sodium starch glycolates, pregelatinized starches, clays (magnesium aluminum silicate), celluloses (such as crosslinked sodium carboxymethylcellulose and microcrystalline cellulose), alginates, pregelatinized starches (i.e. corn starch, etc.), gums (i.e. agar, guar, locust bean, karaya, pectin, and tragacanth gum), cross-linked polyvinylpyrrolidone and the like. Suitable lubricants and antiadherents include, but are not limited to, stearates (magnesium, calcium and sodium), stearic acid, talc waxes, stearowet, boric acid, sodium chloride, DL-leucine, carbowax 4000, carbowax 6000, sodium oleate, sodium benzoate, sodium acetate, sodium lauryl sulfate, magnesium lauryl sulfate and the like. Suitable gildants include, but are not limited to, talc, cornstarch, silica (i.e. CAB-O-SIL ™ silica available from Cabot, SYLOID ™ silica available from W.R. Grace/Davison, and AEROSIL ™ silica available from Degussa) and the like. Sweeteners and flavorants may be added to chewable solid dosage forms to

improve the palatability of the oral dosage form. Additionally, colorants and coatings may be added or applied to the solid dosage form for ease of identification of the drug or for aesthetic purposes. These carriers are formulated with the pharmaceutical active to provide an accurate, appropriate dose of the pharmaceutical active with a therapeutic release profile.

Generally these carriers are mixed with the pharmaceutical active to form a solid preformulation composition containing a homogeneous mixture of the pharmaceutical active of the present invention, or a pharmaceutically acceptable salt thereof. Generally the preformulation will be formed by one of three common methods: (a) wet granulation, (b) dry granulation and (c) dry blending. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from about 0.01 mg to about 500 mg of the active ingredient of the present invention. The tablets or pills containing the novel compositions may also be formulated in multilayer tablets or pills to provide a sustained or provide dual-release products. For example, a dual release tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric materials such as shellac, cellulose acetate, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, methacrylate and ethylacrylate copolymers and the like. Sustained release tablets may also be made by film coating or wet granulation using slightly soluble or insoluble

substances in solution (which for a wet granulation acts as the binding agents) or low melting solids a molten form (which in a wet granulation may incorporate the active ingredient). These materials include natural and synthetic polymers waxes, hydrogenated oils, fatty acids and alcohols (i.e. beeswax, carnauba wax, cetyl alcohol, cetylstearyl alcohol, and the like), esters of fatty acids metallic soaps, and other acceptable materials that can be used to granulate, coat, entrap or otherwise limit the solubility of an active ingredient to achieve a prolonged or sustained release product.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, but are not limited to aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable suspending agents for aqueous suspensions, include synthetic and natural gums such as, acacia, agar, alginate (i.e. propylene alginate, sodium alginate and the like), guar, karaya, locust bean, pectin, tragacanth, and xanthan gum, cellulosics such as sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose, and combinations thereof, synthetic polymers such as polyvinyl pyrrolidone, carbomer (i.e. carboxypolymethylene), and polyethylene glycol; clays such as bentonite, hectorite, attapulgite or sepiolite; and other pharmaceutically acceptable suspending agents such as lecithin, gelatin or the like. Suitable surfactants include but are not limited to sodium docusate, sodium lauryl sulfate, polysorbate, octoxynol-9, nonoxynol-10, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polyoxamer 188, polyoxamer 235 and combinations thereof. Suitable deflocculating or dispersing agent include pharmaceutical grade lecithins. Suitable flocculating agent include but are not limited to simple neutral electrolytes (i.e. sodium chloride, potassium, chloride, and the like), highly charged insoluble polymers and polyelectrolyte

species, water soluble divalent or trivalent ions (i.e. calcium salts, alums or sulfates, citrates and phosphates (which can be used jointly in formulations as pH buffers and flocculating agents). Suitable preservatives include but are not limited to parabens (i.e. methyl, ethyl, *n*-propyl and *n*-butyl), sorbic acid, thimerosal, quaternary ammonium salts, benzyl alcohol, benzoic acid, chlorhexidine gluconate, phenylethanol and the like. There are many liquid vehicles that may be used in liquid pharmaceutical dosage forms, however, the liquid vehicle that is used in a particular dosage form must be compatible with the suspending agent(s). For example, nonpolar liquid vehicles such as fatty esters and oils liquid vehicles are best used with suspending agents such as low HLB (Hydrophile-Lipophile Balance) surfactants, stearalkonium hectorite, water insoluble resins, water insoluble film forming polymers and the like. Conversely, polar liquids such as water, alcohols, polyols and glycols are best used with suspending agents such as higher HLB surfactants, clays silicates, gums, water soluble cellulosics, water soluble polymers and the like. For parenteral administration, sterile suspensions and solutions are desired. Liquid forms useful for parenteral administration include sterile solutions, emulsions and suspensions. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

Furthermore, compounds of the present invention can be administered in an intranasal dosage form via topical use of suitable intranasal vehicles or via transdermal skin patches, the composition of which are well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the administration of a therapeutic dose will, of course, be continuous rather than intermittent throughout the dosage regimen.

Compounds of the present invention can also be administered in a form suitable for intranasal or inhalation therapy. For such therapy, compounds of the present invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped or as an

aerosol spray from a pressurized container or a nebulizer (such as, a metered dose inhaler, a dry powder inhaler or other conventional or non-conventional modes or devices for inhalation delivery) using a suitable propellant (such as, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (such as, those made from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, multilamellar vesicles and the like. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, phosphatidylcholines and the like.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include, but are not limited to polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyl eneoxidepolylysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, to homopolymers and copolymers (which means polymers containing two or more chemically distinguishable repeating units) of lactide (which includes lactic acid d-, l- and meso lactide), glycolide (including glycolic acid), ε-caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-

dioxan-2-one), alkyl derivatives of trimethylene carbonate, δ-valerolactone, β-butyrolactone, γ-butyrolactone, ε-decalactone, hydroxybutyrate, hydroxyvalerate, 1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels and blends thereof.

The therapeutically effective amount of a compound or composition thereof may be from about 0.001 mg/Kg/dose to about 300 mg/Kg/dose. Preferably, the therapeutically effective amount may be from about 0.001 mg/Kg/dose to about 100 mg/Kg/dose. More preferably, the therapeutically effective amount may be from about 0.001 mg/Kg/dose to about 50 mg/Kg/dose. Most preferably, the therapeutically effective amount may be from about 0.001 mg/Kg/dose to about 30 mg/Kg/dose. Therefore, the therapeutically effective amount of the active ingredient contained per dosage unit (e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like) as described herein will be in the range of from about 1 mg/day to about 21,000 mg/day for a subject, for example, having an average weight of 70 Kg. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease condition. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level. Advantageously, compounds of the present invention may be administered in a

single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily.

Representative IUPAC names for the compounds of the present invention were derived using the ACD/LABS SOFTWARE™ Index Name Pro Version 4.5 nomenclature software program provided by Advanced Chemistry Development, Inc., Toronto, Ontario, Canada.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

Boc	=	*tert*-butoxycarbonyl
BuLi	=	*n*-butyllithium
Cpd	=	compound
DCC	=	dicyclohexylcarbodiimide
h	=	hour/hours
HOBT	=	hydroxybenzotriazole
KH	=	potassium hydride
MeI	=	methyliodide
NT	=	not tested
rt/RT	=	room temperature
TFA	=	trifluoroacetic acid
TMSBr	=	bromotrimethylsilane

General Synthetic Methods

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and are illustrated more particularly in the scheme that follows. Since the scheme is an illustration, the invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

Scheme A

Scheme A is illustrative of a general method for the preparation of compounds

of the invention by addition of a phosphonate or phosphinate anion, prepared from a phosphonate or phosphinate Compound **A2**, and an organometallic base such as *n*-butyllithium, to an anhydride Compound **A1** in a solvent such as THF to afford a ketophosphonate or ketophosphinate Compound **A3**, wherein Z is hydrogen, Y is not present and X is one oxygen substituent attached by a double-bond to the carbon in the position β to R_4.

Other compounds of the present invention may be obtained from Compound **A3** using standard ketone manipulations wherein the β position carbon may be reduced from the ketone to a compound of Formula (I) wherein X and Y are both present or wherein Z is a bond. Examples of ketone manipulations include, but are not limited to, the use of 1) organometallic reagents to form alkoxy groups; 2) hydroxyl amines to form imino groups; and, 3) Lawesson's reagent to substitute a thio group in place of the ketone (with appropriate protecting groups added to the COOH group shown).

Compound **A2**, wherein R_6 is as previously defined, can be made according to known methods, such as those described in Katritsky, et. al., *Org. Prep. Proced. Int.*, **1990**, *22*(2), 209-213; *J. Am. Chem. Soc.*, **2002**, *124*, 9386-9387; and, *Chem. Ber.*, **1963**, *96,* 3184-3194. In an embodiment of a general synthetic method, the R_5 substitutent of Compound **A4** is hydrogen and the R_6 substitutent is ethoxy.

Compound **A2**, wherein R_4 is heteroaryl, can be prepared from commercially available or known haloalkyl substituted heteroaryl starting materials (such as 3-bromomethyl-5-Cl-benzothiophene used to prepare Cpd **33**) using techniques known to those skilled in the art.

Compound **A3** may be coupled to the R_1 portion of Formula (I) using standard coupling reactions. For example, when R_1 is a secondary amine in a heterocyclyl ring, the nitrogen on the ring may be coupled to Compound **A3**

(similar to the reaction shown in Scheme A, e.g. the ring nitrogen in Compound **A4** would be coupled with Compound **A8**). Appropriate blocking groups can be employed to minimize undesirable side reactions. Analogous coupling reactions with Compound **A3** can be performed when R_1 is $N(R_7R_8)$ to couple the substituted amine to the carboxylic acid of Compound **A3**. In one embodiment of the present invention the coupling reaction of Compound **A3** with R_1 when R_1 is $N(R_7R_8)$ and R_8 is a heterocycle is provided to further illustrate the present invention.

In Scheme A, the reaction of a suitably protected amino substituted heterocycle Compound **A4** (wherein the protected amino is substituted with a hydrogen atom for R_7 and an unsubstituted ad). heterocycle for R_8) with a Q-substituted R_{8a} Compound **A5** (wherein Q is a suitable leaving group (such as , but not limited to, a halogen atom) and R_{8a} is a substituent as previously defined in the R_8 ba).-bl) list) in a solvent such as DMF containing a base (such as, but not limited to, triethylamine) provided an R_{8b} substituted Compound **A6**.

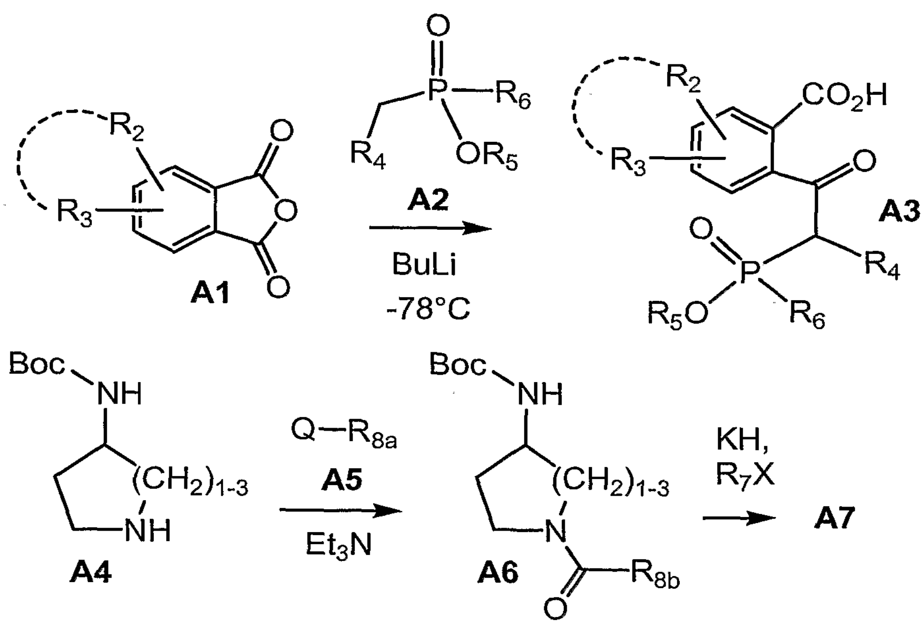
In an embodiment of a general synthetic method, the heterocyclyl portion of Compound **A4** was further substituted on a nitrogen ring atom by reaction with an acid chloride Compound **A5**, wherein the Q portion was chlorine and wherein the R_{8a} portion was bc). carbonyl substituted with an R_{8b} substituent selected from C_{1-8}alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, heteroaryl, heteroaryl(C_{1-8})alkyl or heteroaryl(C_{2-8})alkenyl. In an alternate embodiment, the reaction may performed by reaction with an acid chloride Compound **A5**, wherein the Q portion is chlorine and wherein the R_{8a} portion is bl). sulfonyl substituted with an R_{8b} substituent; wherein R_{8b} is as previously defined.

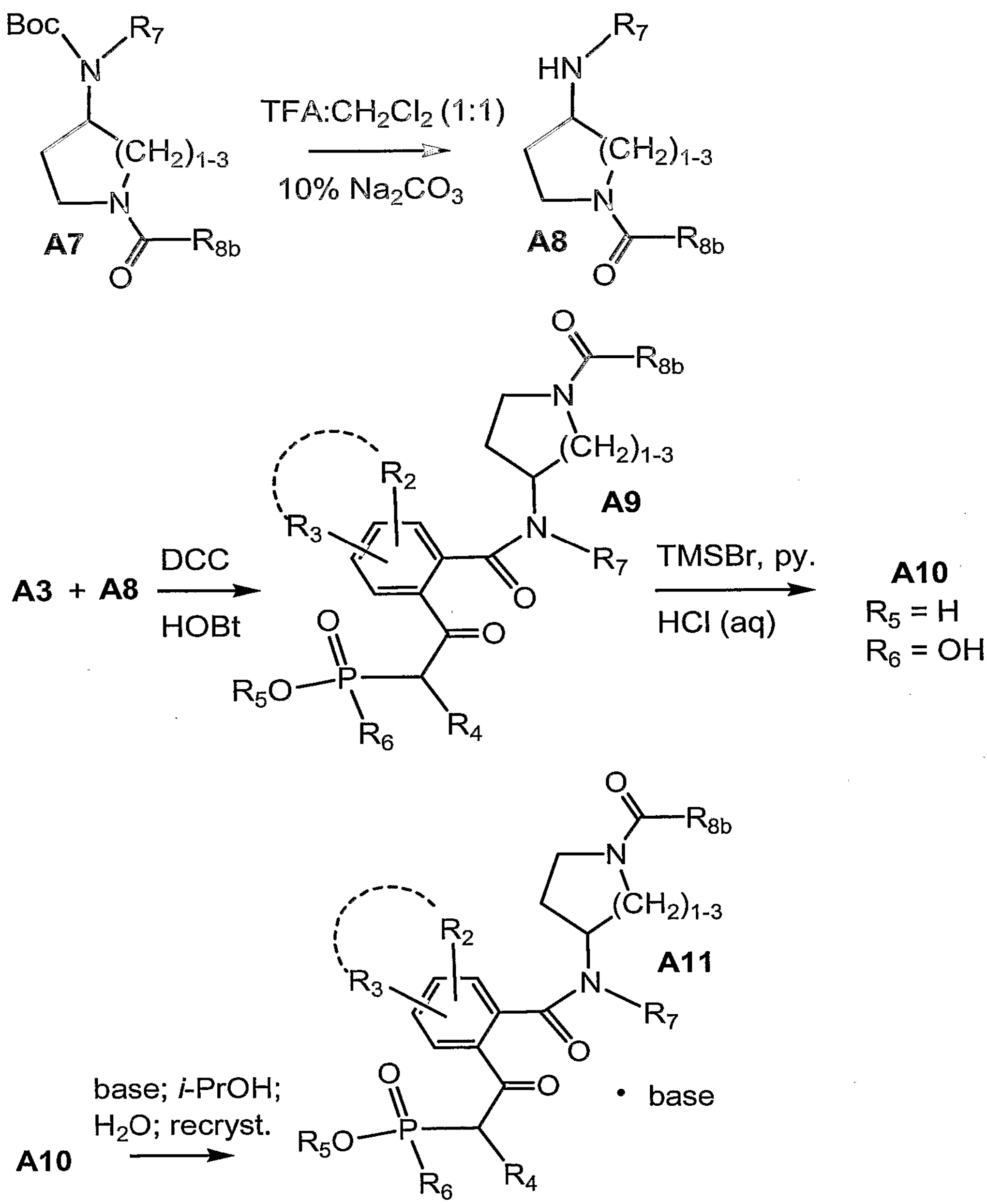
Treatment of Compound **A6** with a base such as potassium hydride followed by treatment with an R_7X alkylating agent such as iodomethane in a solvent such as THF yielded Compound **A7**. The amine Compound **A8** can be obtained from Compound **A7** by removal of the Boc protecting group upon treatment

with an acid such as TFA in a solvent such as CH_2Cl_2. The free base of Compound **A8** is obtained upon treatment with a base such as aqueous Na_2CO_3.

Compound **A9** can be prepared by a standard coupling procedure between Compound **A3** and Compound **A8** using routine reagents such as DCC and HOBT in a solvent such as CH_3CN. Dealkylation of Compound **A9** with reagent such as bromotrimethylsilane in a solvent such as pyridine, followed by treatment with dilute HCl afforded Compound **A10** (wherein, in an embodiment of a general synthetic method, the R_5 ethyl group and the R_6 ethoxy group were replaced with hydrogen). A salt of Compound **A10** such as target Compound **A11** can be prepared by treating Compound **A10** with a monobasic or dibasic amine such as tris(hydroxymethyl)aminomethane in a solvent system such as i-PrOH and water.

Scheme A





Scheme B

Scheme B is illustrative of an alternative general synthetic method for the preparation of compounds of the invention by addition of a Compound **A2** (in an embodiment of an alternative general method, the R_5 substitutent of Compound **A2** is ethyl and the R_6 substitutent is ethoxy) and R"M (wherein R"M represents an organometallic reagent such as LiHMDS (lithium

hexamethyldisilylazide), lithium tetramethylpiperidide or NaHMDS (sodium hexamethyldisilazide)) to an anhydride Compound **A1**.

The reaction is subsequently quenched with 6N HCl to a pH between 4 and 6 to afford an enol Compound **B1**, wherein for a compound of Formula (I), Z is a bond, Y is not present and X is one oxygen substituent attached by a single-bond to the carbon in the position β to R_4. Other compounds of the present invention may be obtained from Compound **B1** using standard ketone manipulation wherein the enol double bond may be reduced to the ketone; wherein for a compound of Formula (I), Y is not present and X is one oxygen substituent attached by a double-bond on the β position carbon. A coupling reagent (such as, but not limited to, chloroformates (such as, but not limited to, isobutyl chloroformate), cyanuric chloride, methanesulfonyl chloride, or diethyl chlorophosphate) may then be employed for ring closure to form a substituted lactone intermediate Compound **B2** in the presence of a base such as, but not limited to, Et_3N.

Reaction of a dihydroxy substituted heterocycle Compound **B3** (or other ketones and other protected ketones) with a Q-substituted R_{8a} Compound **A5** in a solvent (such as, but not limited to, CH_2Cl_2, THF or mixtures thereof) containing a base (such as, but not limited to, sodium bicarbonate, potassium carbonate) provided an R_{8b} substituted Compound **B4**.

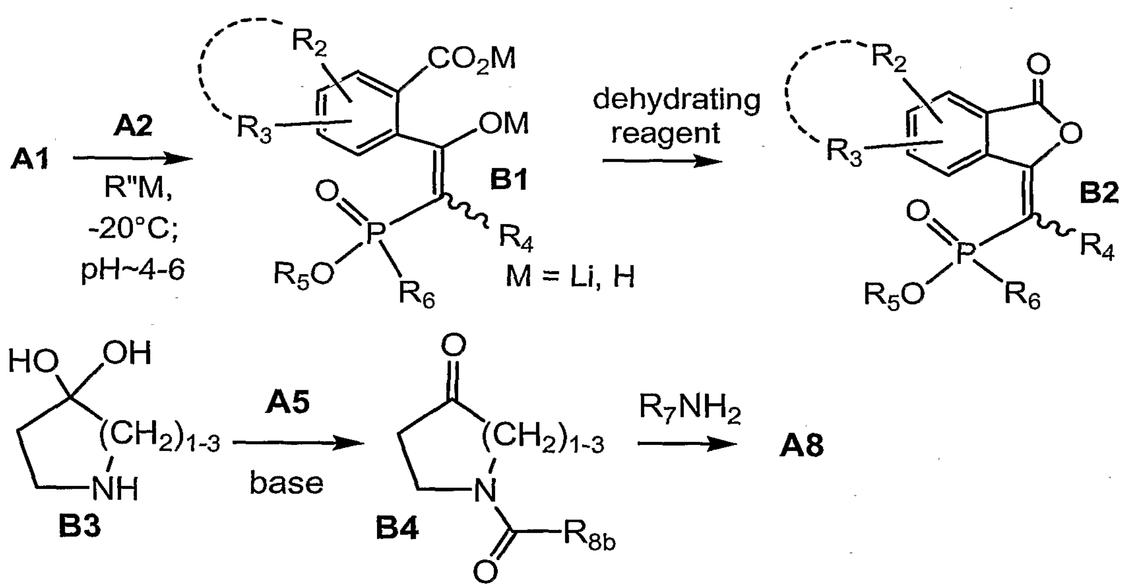
Compound **B4** was treated with R_7NH_2 in a solvent (such as, but not limited to, CH_2Cl_2, THF or mixtures thereof) then subjected to reductive amination or hydrogenation using a hydride reducing agent (such as, but not limited to, $NaBH(OAc)_3$, or hydrogenation with Pd, Pt or Ni catalyst). The free base of Compound **A8** was obtained upon quenching the reaction with a base such as aqueous Na_2CO_3.

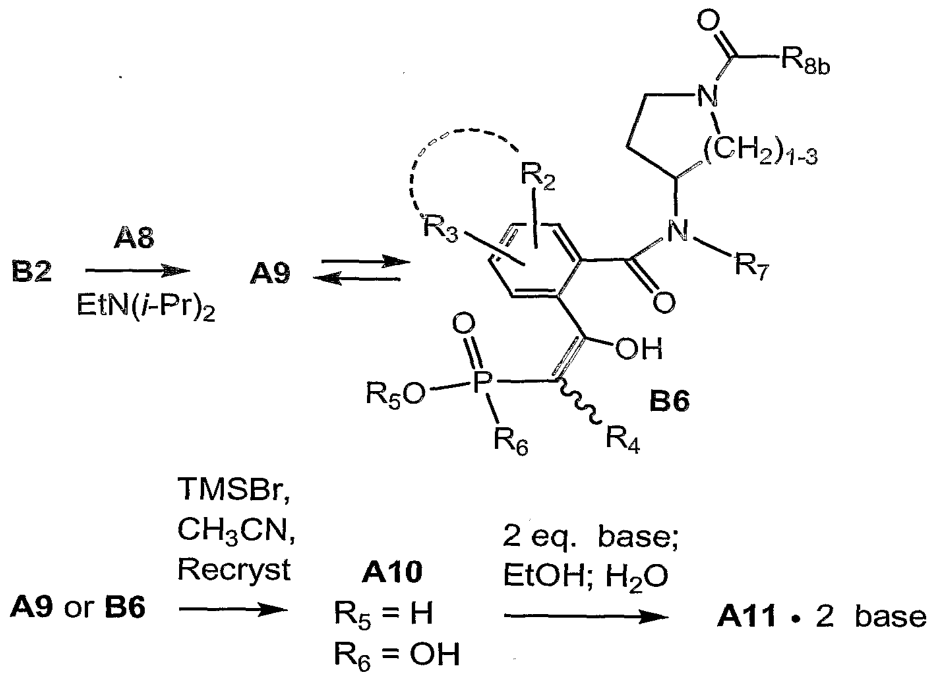
Compound **A9** (in tautomeric equilibrium with Compound **B6**) was prepared by

opening the 5-membered lactone ring intermediate Compound **B2** with Compound **A8** (or Compound **B5**, a salt of Compound **A8**) in the presence of DIEA (diisopropylethylamine) in a solvent (such as, but not limited to, acetone or MEK (methylethyl ketone)).

Dealkylation of the equilibrium mixture of Compound **A9**-Compound **B6** with a reagent (such as, but not limited to, TMSBr (bromotrimethylsilane) or TMSI) in a solvent (such as, but not limited to, CH_3CN or pyridine), followed by recrystallization afforded Compound **A10** (wherein the R_5 ethyl group is replaced with hydrogen and the R_6 ethoxy group is replaced with hydroxy). A salt of Compound **A10** such as Compound **A11** (and tautomers thereof) was prepared by treating Compound **A10** with a diamine such as tris(hydroxymethyl)aminomethane in a solvent system such as a mixture of EtOH and water.

Scheme B





Scheme C

Scheme C is illustrative of an alternative method for the preparation of the intermediate Compound **B2**, wherein the enol Compound **B1** is protonated to the free acid ketone Compound **A3** by adjusting the pH to about pH 1, followed by intramolecular dehydration to provide the target lactone intermediate Compound **B2.**

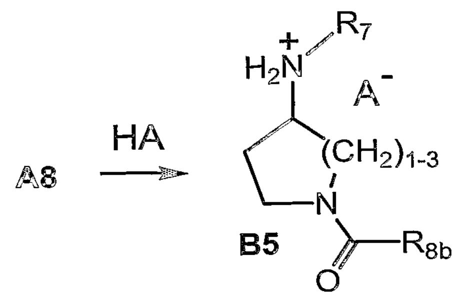
Scheme C

$$\mathbf{B1} \xrightarrow{\text{pH\sim1}} \mathbf{A3} \xrightarrow{\text{dehydrating reagent}} \mathbf{B2}$$

Scheme D

Scheme D is illustrative of a method for the preparation of an acid addition compound **B5**, wherein Compound **A8** is reacted with an acid HA (such as, but not limited to, HCl, HBr or *p*-toluenesulfonic acid) to provide the target Compound **B5** which may be carried forward in place of Compound **A8** in the reaction with Compound **B2**.

Scheme D

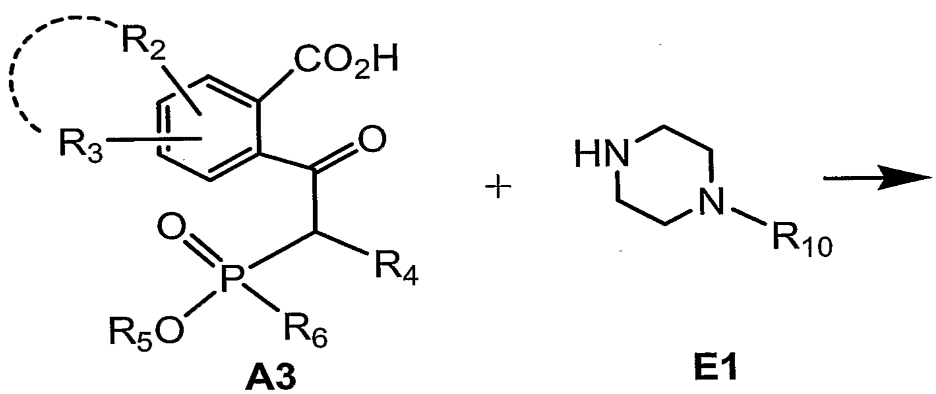


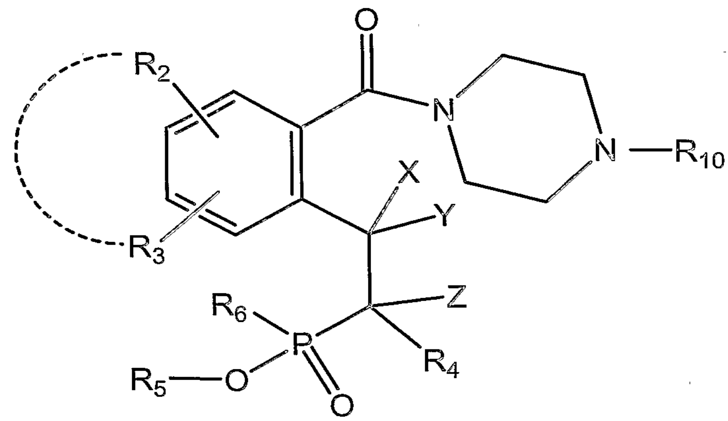
<u>Scheme E</u>

Scheme E is illustrative of a method of the preparation of compounds of Formula (II).

Compound **A3** may be reacted with a compound of **E1** under appropriate conditions to couple the compounds via an amide linkage. For example a salt can be formed from **E1** and reacted with **A3** to form an ammonium salt of the carboxylic acid that can be dehydrated to form the amide linkage.

Scheme E





Formula (II)

Compound **E1** can be prepared from commercially available or known starting materials using techniques known to those of skill in the art.

Specific Synthetic Examples

Specific compounds which are representative of this invention were prepared as per the following examples and reaction sequences; the examples and the diagrams depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the invention and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The depicted intermediates may also be used in subsequent examples to produce additional compounds of the present invention. These reactions can be further optimized to increase the yields. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

All chemicals were obtained from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300B (300 MHz proton) or a Bruker AM-400 (400 MHz proton) spectrometer with Me_4Si as an internal standard (s = singlet, d = doublet, t = triplet, br = broad). APCI-MS and ES-MS were recorded on a VG Platform II mass

spectrometer.

Example 1

[2-[3-[[methyl[1-(2-naphthalenylcarbonyl)-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid (Compound **2**)

To a solution of 2.5M *n*-BuLi in hexanes (40 mL, 0.1mol) in 70 mL of THF at -78°C was added dropwise a solution of 1-naphthyldiethylphosphonate (Compound **1A**, 28 g, 0.1 mol) in 60 mL THF over 30 min. After stirring for an additional 30 min, 2,3-naphthalenedicarboxylic anhydride (Compound **1B**, 20 g, 0.1 mol) was added portionwise via solid-addition funnel to the mixture over 20 min. After the addition was complete, the slurry was allowed to reach 0°C gradually where it was held for another 1.5 h. Excess NH_4Cl (sat'd., aq.) was added, and the mixture was filtered through a pad of Celite 545. The filtrate was extracted with 200 mL of EtOAc and the layers were separated. The organic phase was concentrated (without drying) under reduced pressure at rt and the residue was triturated 4X with boiling ether. The residue was treated with 200 mL of EtOAc and adjusted to pH 3 with 2N HCl (aq.) with vigorous stirring. The layers were separated, and the organic phase was washed once with H_2O, dried (Na_2SO_4) and concentrated to afford 24 g of Compound **1C** as a white powder: MS (ES) MH+ = 477; HPLC: 3.68 min.

To a solution of Compound **1D** (4 g, 20 mmol) containing 3.1 mL of triethylamine (22 mmol) in 45 mL of DMF was added Compound **1E** (3.8 g, 20 mmol). After stirring overnight, the mixture was filtered and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and washed sequentially with H_2O, Na_2CO_3 (10%, aq.), H_2O, $KHSO_4$ (1N aq.) and H_2O. The organic phase was dried (Na_2SO_4), and concentrated to afford 6.0 g of Compound **1F** as a foam: MS (ES) MH^+ = 355.

Potassium hydride (2.3 g of a 35% oil dispersion; 20 mmol) was washed with

hexanes, then treated with 30 mL of THF and cooled to 0 °C. To the suspension was added dropwise a solution of Compound **1F** (5.9 g, 16.8 mmol) in 15 mL of THF. The mixture was stirred at 0°C for 0.5 h, then stirred an additional 0.5 h at rt. The mixture was cooled to 0°C and iodomethane (15.7 g, 100 mmol) was added dropwise. The mixture was stirred at 0°C for 0.5 h then warmed to rt and stirred an additional 1.5 h. Excess 10% Na_2CO_3 (aq) was added slowly at 0°C, and the volatiles were removed under reduced pressure. The aqueous layer was extracted 3 times with EtOAc and the combined extracts were dried (Na_2SO_4) and concentrated to yield 6.1 g of Compound **1G** as foam. HPLC R_t = 3.76 min, 100%; MS (ES) MH+ = 369.

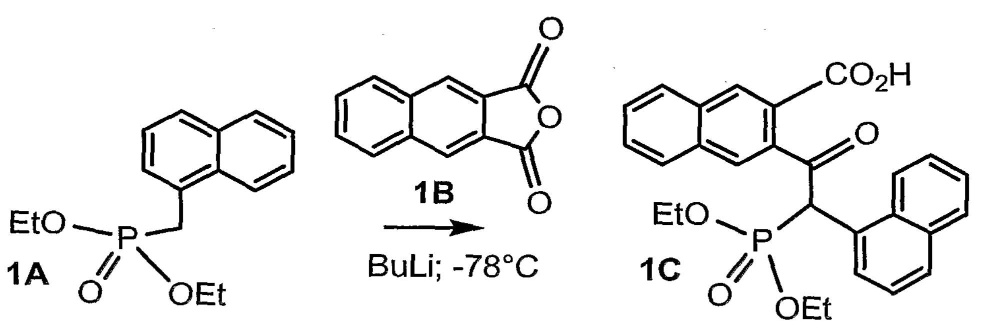
A solution of Compound **1G** (6.1 g, 16.5 mmol) was dissolved in 15 mL of a 1:1 solution of TFA:CH_2Cl_2 and stirred for 1 h at rt. Volatiles were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 and treated with excess 10% Na_2CO_3 (aq). The layers were separated, and the aqueous phase was extracted 3 times with CH_2Cl_2. The organic extracts were combined, dried (Na_2SO_4) and concentrated to afford 4.3 g of Compound **1H** as a viscous oil. HPLC R_t = 1.5 min, 100%; MS (ES) MH^+ = 269.

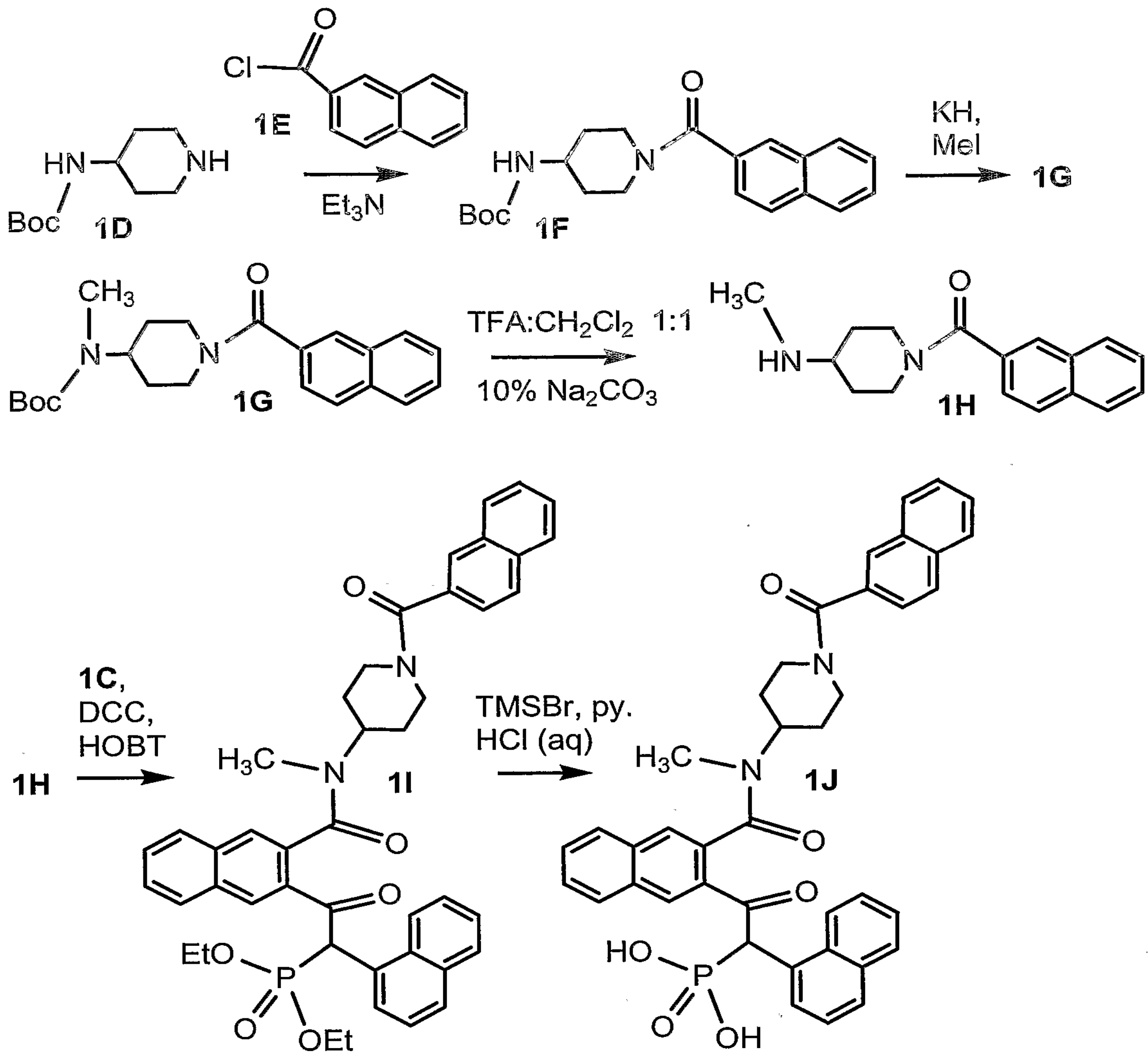
A solution of Compound **1C** (4.9 g, 10.3 mmol), Compound **1H** (3.3 g, 12.3 mmol) and HOBT (2.1 g, 15.4 mmol) in 100 mL CH_3CN was treated with a solution of DCC (2.5 g, 12.3 mmol) in 7 mL of CH_3CN. After stirring for 12 h, 5 mL of DIPEA was added and the reaction was stirred for an additional 48 h. The mixture was filtered and concentrated. The residue was purified by flash column chromatography (silica: CH_2Cl_2:MeOH ramped from 98:1 to 95:5) to yield 6.9 g of Compound **1I**. HPLC R_t = 4.3 min; MS (ES) MH+ = 727.

To a solution of Compound **1I** in 15 mL of pyridine was added 5 mL of bromotrimethylsilane. The mixture was stirred for 15 min, then concentrated under reduced pressure. The residue was treated with excess 3N HCl(aq), then stirred for 3h. The white precipitate was collected and rinsed with water,

then triturated with CH_3CN to afford 5.1g of Compound **1J**. HPLC R_t = 3.6 min; MS (ES) MH+ = 671. To a solution of Compound **1J** in 50 mL of CH_3CN was added a solution of tris(hydroxymethyl)aminomethane (0.9 g, 7.7 mmol) in 7 mL of H_2O. The solution was filtered and the filtrate lyophilized after partial concentration to remove most of the CH_3CN. The resulting white solid was recrystallized from *i*-PrOH to yield 5.5 g of Compound **2** as an off-white solid. HPLC: R_t = 3.6 min; 100%; MS (ES) MH+ = 671; Anal. Calc'd for $C_{40}H_{35}N_2O_6P$•1.0 $C_4H_{11}NO_3$•1.0 *i*-PrOH• 1.5 H_2O: C, 64.23; H, 6.54; N, 4.79; H_2O, 3.08. Found: C, 63.93; H, 6.40; N, 4.85; H_2O, 2.74.

For Example1, TLC was performed using Whatman 250-µm silica gel plates. Preparative TLC was performed with Analtech 1000-µm silica gel GF plates. Flash column chromatography was conducted with flash column silica gel (40-63 µm) and column chromatography was conducted with standard silica gel. HPLC separations were carried out on three Waters PrepPak® Cartridges (25 x 100 mm, Bondapak® C18, 15-20 µm, 125 Å) connected in series; detection was at 254 nm on a Waters 486 UV detector. Analytical HPLC was carried out on a Supelcosil ABZ+PLUS column (5 cm x 2.1 mm), with detection at 254 nm on a Hewlett Packard 1100 UV detector. Microanalysis was performed by Robertson Microlit Laboratories, Inc.




1E
Cl
O
HN
NH
Boc
1D
Et3N
1F
KH,
MeI
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CH3
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1H
1C,
DCC,
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HCl (aq)
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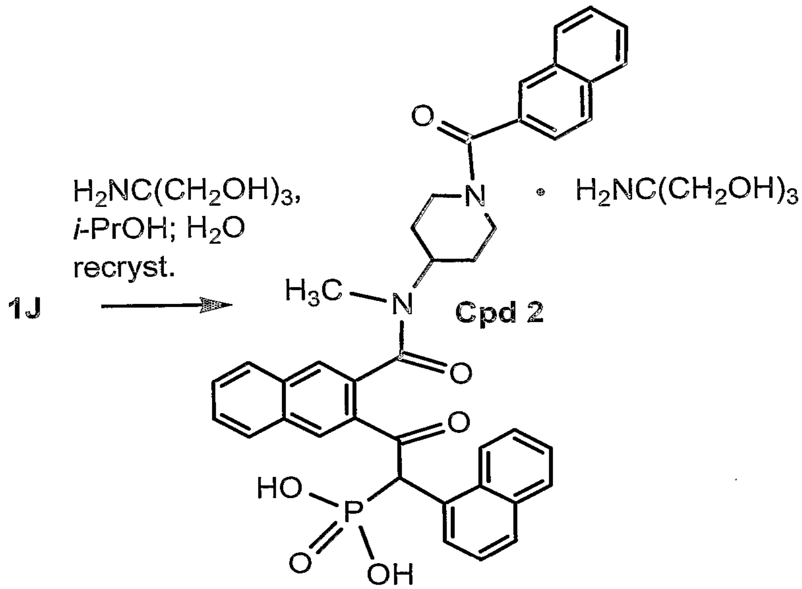


Following the procedure of Example 1 and substituting the appropriate starting materials, compounds and reagents, the following Compounds 1 and 3-33 of the invention were also prepared:

Cpd	Name	MS m/e (MH^+).
(1)	[2-[3-[[methyl(4-phenylcyclohexyl)amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	592
(3)	[2-[3-[[[1-[(6-methoxy-2-naphthalenyl)carbonyl]-3-pyrrolidinyl]methylamino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	687
(4)	[2-[3-[[[1-[(6-bromo-2-naphthalenyl)carbonyl]-4-piperidinyl]methylamino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	771 (M^{+Na})
(5)	[2-[3-[[[1-[(2*E*)-3-(4-fluorophenyl)-1-oxo-2-propenyl]-3-pyrrolidinyl]methylamino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	651
(6)	[2-[3-[[methyl[1-[(2*E*)-1-oxo-3-phenyl-2-propenyl]-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	647
(7)	[1-(1-naphthalenyl)-2-oxo-2-[3-[(4-phenyl-1-piperidinyl)carbonyl]-2-naphthalenyl]ethyl]-phosphonic acid	564
(8)	[1-(1-naphthalenyl)-2-oxo-2-[3-[(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl)carbonyl]-2-naphthalenyl]ethyl]-	634

	phosphonic acid	
(9)	[2-[3-[[methyl[1-[(2*E*)-3-(4-methylphenyl)-1-oxo-2-propenyl]-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	661
(10)	[2-[3-[[methyl[1-[(2*E*)-1-oxo-3-[4-(trifluoromethyl)phenyl]-2-propenyl]-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	715
(11)	[2-[3-[[methyl[1-(2-naphthalenylcarbonyl)-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-2-oxo-1-phenylethyl]-phosphonic acid	621
(12)	[2-[3-[[4-(4-methoxyphenyl)-1-piperidinyl]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	594
(13)	[2-[3-[[[1-[(2*E*)-3-[4-(dimethylamino)phenyl]-1-oxo-2-propenyl]-4-piperidinyl]methylamino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	690
(14)	[2-[3-[[4-(3-methoxyphenyl)-1-piperidinyl]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	594
(15)	[2-[3-[[(1-benzoyl-4-piperidinyl)methylamino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	621
(16)	[2-[3-[[4-(2-benzothiazolyl)-1-piperidinyl]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	621
(17)	[2-[3-[(cyclohexylmethylamino)carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	516
(18)	[2-[3-[[methyl[1-[1-oxo-3-[4-(trifluoromethyl)phenyl]propyl]-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	717
(19)	[1-(1-naphthalenyl)-2-oxo-2-[3-[(3-phenyl-1-pyrrolidinyl)carbonyl]-2-naphthalenyl]ethyl]-phosphonic acid	550
(20)	[2-[3-[[methyl[1-(2-methyl-1-oxopropyl)-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	587
(21)	[2-[3-[(cyclopentylmethylamino)carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	502
(22)	[2-[3-[[[4-(1,1-dimethylethyl)cyclohexyl]methylamino]carbonyl]-2-	572

	naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	
(23)	[2-[3-[[methyl[1-(2-naphthalenylcarbonyl)-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid methyl ester	685
(24)	[2-[3-[[[1-[(6-hydroxy-2-naphthalenyl)carbonyl]-4-piperidinyl]methylamino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	687
(25)	[1-(1-naphthalenyl)-2-oxo-2-[3-[[3-(2-phenylethyl)-1-pyrrolidinyl]carbonyl]-2-naphthalenyl]ethyl]-phosphonic acid	578
(26)	[2-[3-[[(1-acetyl-4-piperidinyl)methylamino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	559
(27)	[2-[3-[[methyl(4-methylcyclohexyl)amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	530
(28)	[2-[1-[[methyl(tricyclo[3.3.1.$1^{3,7}$]dec-1-ylmethyl)amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	582
(29)	[2-[3-[[methyl(4-phenyl-3-cyclohexen-1-yl)amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	590
(30)	[1-(1-naphthalenyl)-2-[3-[[[1-(2-naphthalenylcarbonyl)-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-2-oxoethyl]-phosphonic acid	657
(31)	[2-[2-[[methyl[1-(2-naphthalenylcarbonyl)-4-piperidinyl]amino]carbonyl]phenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphonic acid	621
(32)	methyl[2-[3-[[methyl[1-(2-naphthalenylcarbonyl)-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-1-(1-naphthalenyl)-2-oxoethyl]-phosphinic acid	669
(33)	[1-(5-chlorobenzo[*b*]thien-3-yl)-2-[3-[[methyl[1-(2-naphthalenylcarbonyl)-4-piperidinyl]amino]carbonyl]-2-naphthalenyl]-2-oxoethyl]-phosphonic acid	712

Example 2

*Alternative Method of Synthesis for Compound **2***

THF (tetrahydrofuran) (1081.0 mL) and 1-naphthyldiethylphosphonate Compound **2B** (223.0 gm, 0.7612 mol) were combined in a flask and cooled to

about -20 °C using a dry ice-methanol cooling bath. A solution of 1M LiHMDS (1597.0 mL, 1.597 mol) in THF was added to the cooled mixture while keeping the temperature at about -20 °C to form a fine slurry which was stirred for an additional 30 minutes. A 2,3-naphthalinedicarboxylic anhydride Compound **2A** (158.80 gm, 0.7612 mol) was added portionwise over about a 1 h period while keeping the temperature of the mixture at about -20 °C. The addition funnel and flask walls were rinsed with THF (100.0 mL), the cooling bath was removed and the mixture temperature raised to about 5 °C for about 1.5 h. Once the reaction was complete (as shown by HPLC), the final pH of the mixture was adjusted to about pH 5 by slowly adding 6N HCl (422 mL, 2.34 mol) while the temperature of the mixture was maintained at about 5 °C. The mixture was stirred for about 30 min more at about 5 °C to provide a crude product as a fine white solid. The crude product was filtered using a porcelain filter. The wet solid was then washed with water (1000.0 mL), left to filter overnight, then dried at 70 °C to provide a dilithium salt Compound **2C** (365.1 gms; mass yield: 100.6%). Compound **2C** was used in the next step without further purification.

Methanol (2500.0 mL) and water (360.0 mL) were added to a flask and stirred. Compound **2C** (365.1 gm, 0.7612 mol) was added to the stirring solution and the flask was rinsed with methanol (100.0 mL) to form a slurry. The slurry was stirred at RT for 30 minutes and then 12 N HCl (80.0 mL, 0.960 mol) was added over a 2 min period as the slurry turned into a hazy solution. The solution was stirred at RT until crystallization began, then was cooled to about 5 °C for 1 h to provide a crude product as a white granular solid. The product was filtered and washed with water (500.0 mL), then dried *in vacuo* overnight at a temperature of about 50 °C to provide Compound **2D** (280 gms; mass yield: 77.3%).

Compound **2D** (199.8 gm) and THF (2 L) were combined in a flask, then agitated and cooled to a temperature of from about 0 °C to about 5 °C. NMM (4-methylmorpholine) (51.5 mL) was added to the flask while the mixture

temperature was maintained at a temperature of from about 0 °C to about 5 °C. The mixture was then agitated for an additional 15 min or until a solution was obtained. IBCF (isobutylchloroformate) (56 mL) was added portionwise while the mixture temperature was maintained at a temperature of from about 0 °C to about 15 °C. When the addition was complete, the mixture temperature was warmed to a temperature of from about 20 °C to about 25 °C, then agitated for 1 h. Once the reaction was complete, the NMM salts were filtered, washed with THF (150 mL) and allowed to dry. The filtrate was then combined with *n*-heptane (2.5 L) over a period of about 10 min and then agitated at a temperature of from about 20 °C to about 25 °C for about 30-45 min. Additional *n*-heptane (1.5 L) was added over a period of about 10 min. The mixture was then cooled to a temperature of from about 0 °C to about 5 °C and aged for about 1.5 h. The resulting suspension was filtered and washed with *n*-heptane (250 mL), allowed to air dry over a period of about 30 min and then dried *in vacuo* overnight at a temperature of from about 45 to about 50 °C to provide Compound **2E** (165 gms; mass yield: 88.4%).

DCM (dichloromethane) (600 mL) and a 2-naphthoyl chloride Compound **2F** (189.0 gm) were combined in a flask and agitated until solubilized. 4-Piperidone hydrate hydrochloride Compound **2G** (150 g) and $NaHCO_3$ (sodium hydrogen carbonate) (260.0 gms) were then added via addition funnel. DCM (300 mL) was used to rinse the funnel and the resulting mixture was agitated for 18 h. Once the reaction was complete (as shown by HPLC), water (2.6 L) was added to the flask and the mixture was stirred vigorously to dissolve the $NaHCO_3$. After a period of about 5 to about 10 minutes, the layers were allowed to separate over a period of about 30 minutes. The aqueous layer was removed. Saturated aqueous $NaHCO_3$ (300 mL) was again added and the mixture agitated for a period of about 5 to about 10 min. The layers were allowed to separate over a period of about 30 min and the aqueous layer was removed. Water (300 mL) was added and the mixture stirred gently for a period of from about 5 to about 10 min. The layers were allowed to separate

over a period of about 30 min and the organic layer (~960 mL) containing Compound **2H** was removed (concentration of Compound **2H** in DCM: 235.98 mg/ mL; calculated mass of Compound **2H** in DCM: 226.54 gms; calculated mass yield: 93.46%).

Compound **2H** (~50 gms, ~265 mg/mL in DCM) and acetic acid (4.9 mL) were combined in a flask and the mixture was cooled to a temperature of from about 0 °C to about 5 °C. 2.0M $MeNH_2$ (methylamine) (296 mL) in THF was added portionwise while maintaining the mixture at a temperature of from about 0 °C to about 19 °C. The mixture was allowed to warm to ambient temperature and was agitated for a period of about 30 min. $NaBH(OAc)_3$ (sodium triacetoxyborohydride) (51.4 gms) was then added portionwise while maintaining the solution at a temperature of from about 19 °C to about 27 °C. The mixture was aged for about 40 min at a temperature of from about ambient to about 27°C. Once the reaction was complete (as shown by HPLC), water (500 mL) was added while maintaining the solution at a temperature of below about 30 °C. Sodium hydroxide (115 mL; 5% w/v in water) was then added to the mixture to raise the pH to from about pH 10 to about pH 11. The mixture was agitated vigorously for a period of from about 3 to about 10 min. The layers were separated and the aqueous layer was removed. Water (143 mL) was added and the mixture agitated for a period of from about 3 to about 10 min. The layers were again separated and the organic layer containing Compound **2I** was removed (concentration of Compound **2I** in DCM: 0.229 mg/ mL; calculated mass of Compound **2I** in DCM: 45.18 gms; mass yield: 85.3%).

Compound **2I** (150 mL, 0.069 mol) was placed in solution with CH_2Cl_2:THF (150 mL; 1:8) and concentrated to a thick oil *in vacuo* while maintaining the mixture at a temperature of about or below 40°C using a cooling bath. 2-Butanone (320 mL) was added portionwise to the thick oil to transfer the oil to another flask. The mixture was agitated and $EtN(i\text{-}Pr)_2$ (diisopropylethylamine) (11.0 mL, 0.063 mol) and Compound **2E** (27.3 gms, 0.057 mol) were added. The

mixture was heated to a temperature of about 65 °C for a period of from about 6 to about 7 h. Once the reaction was complete (as shown by HPLC), the mixture was cooled to ambient temperature and crystallized over a period of from about 72 to about 96 h (the product can take up to 48 h to start to crystallizing, having a cloud point time around 28 h). The product was filtered and washed with acetone (2X 10 mL) (each wash), then dried *in vacuo* overnight at a temperature of about 75 °C to provide Compound **2J** (31.4 gms; yield: 75.1%) as a white powder.

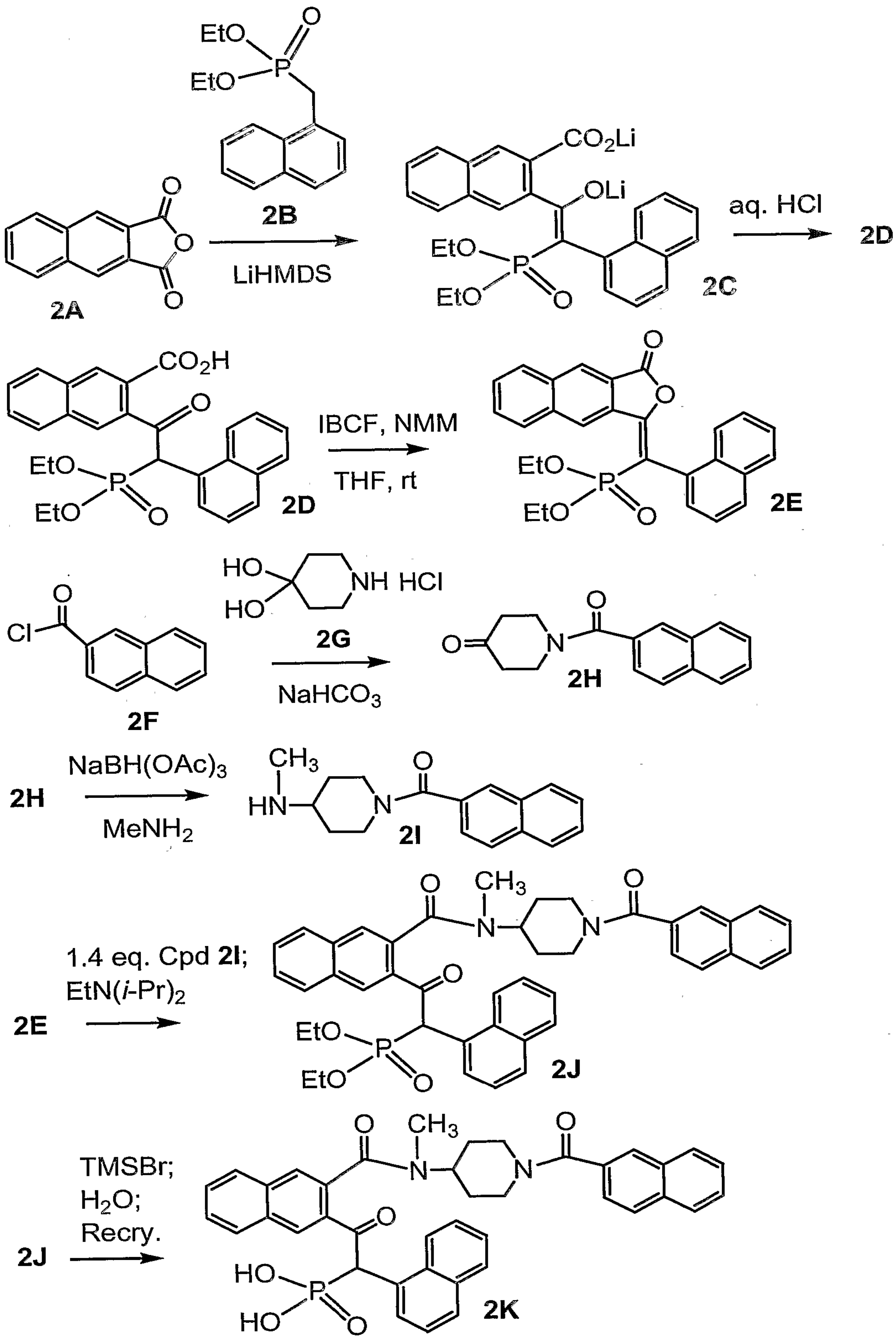
Compound **2J** (10.0 g) and acetonitrile (40 mL) under nitrogen were added to a flask to form a suspension. The suspension was agitated for a period of from about 5 to about 10 min, then bromotrimethylsilane (10 mL) was added via additional funnel over a period of from about 10 to about 15 min at RT. The solution was stirred for at least a time period of about 1 h at rt. Once the reaction was complete (as shown by HPLC), the mixture was transferred to an addition funnel and then added to water (250 mL). The resulting slurry was stirred vigorously during the addition and the temperature maintained at from about 20 °C to about 25 °C. The slurry was further agitated over a period of from about 1 to about 1.5 h, then filtered and washed with water (2X15 mL). The resulting wet cake was then dried *in vacuo* overnight at a temperature of about 40 °C to provide a crude product Compound **2K** (10.2 gms) as a white solid.

Compound **2K** (110.0 gms, 0.127 mol) and methanol (550 mL) were added to a flask to form a slurry. The slurry was stirred at RT over a period of from about 55 to about 60 min (the recrystallization mixture gave a hazy solution within about 5 minutes after adding MeOH and gradually afforded a white suspension after about 30 minutes). An acetone:water (1100 mL; 4:1) solution was added and the suspension was stirred at RT for a period of from about 180 to about 190 min to afford a white solid. The solid was filtered and washed with water (3 X 350 mL), forming a wet cake was then dried *in vacuo* overnight at a

temperature of from about 30 to about 35 °C to provide a recrystallized Compound **2K** (82.3 gms; yield: 96.1%) as a fine white solid.

Recrystallized Compound **2K** (30.0 g, 0.0431 mol) and tris(hydroxymethyl)aminomethane (13.07 g, 0.107 mol; a clear white crystalline solid) were combined in a flask and ethanol (300 mL) and water (30 mL) were added. The solution was agitated to provide a clear solution after a period of about 15 min. A thin suspension was formed after a period of from about 2 to about 3 h and a thick white suspension was formed after a period of from about 3 to about 5 h (the mixture may need to be seeded to enhance crystallization if a thin suspension is not formed after a period of about 3 h). The suspension was stirred at RT for an additional period of about 4 h. The thick suspension was thinned by adding ethanol (180 mL), then filtered and washed with ethanol (120 mL), allowed to air dry over a period of about 30 min and then dried *in vacuo* for a time period of from about 24 to about 67 h at a temperature of about 40 °C to provide Compound **2E** (38.6 gms; yield: 91.8%) as a bis-tromethane salt (ratio of tris(hydroxymethyl)aminomethane:Compound **2E**: 1.99:1).

For Example2, analytical HPLC was carried out using Phenomenex Luna (15 cm x 4.6 mm; 5 μ; detection was at 220 nm), Phenomenex Luna 5μ C18(2) (4.6 mm x 250; detection was at 225 nm) and Synergi 4μ MAX-RP 80A (15 cm x 4.6 mm; detection was at 225 nm) columns. Microanalysis was performed by Quantitative Technologies, Inc.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2C
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2D
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THF, rt
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2G
2F
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2H
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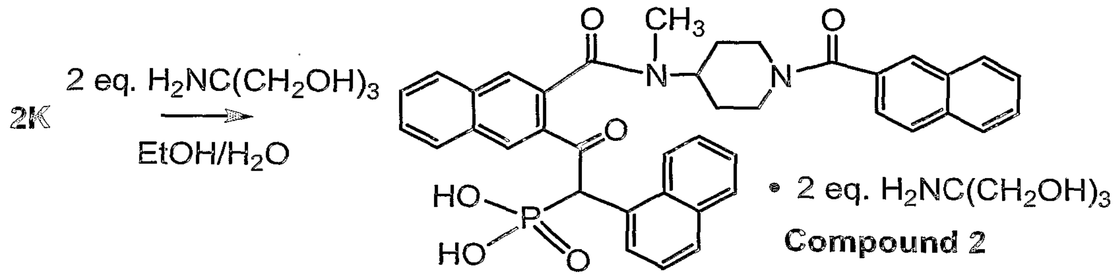
Recry.
2K

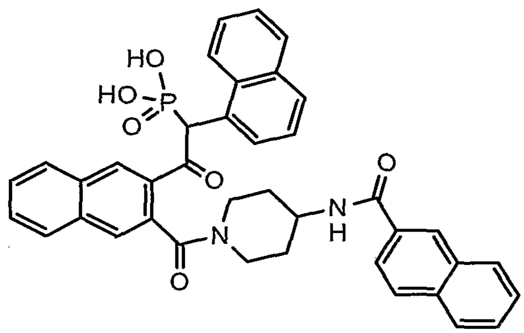


Compound 2

Example 3

As a specific embodiment of an oral composition, 100 mg of the Compound **2** of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

Example 4



[2-(3-{4-[(Naphthalene-2-carbonyl)-amino]-piperidine-1-carbonyl}-naphthalen-2-yl)-1-naphthalen-1-yl-2-oxo-ethyl]-phosphonic acid

Compound 34

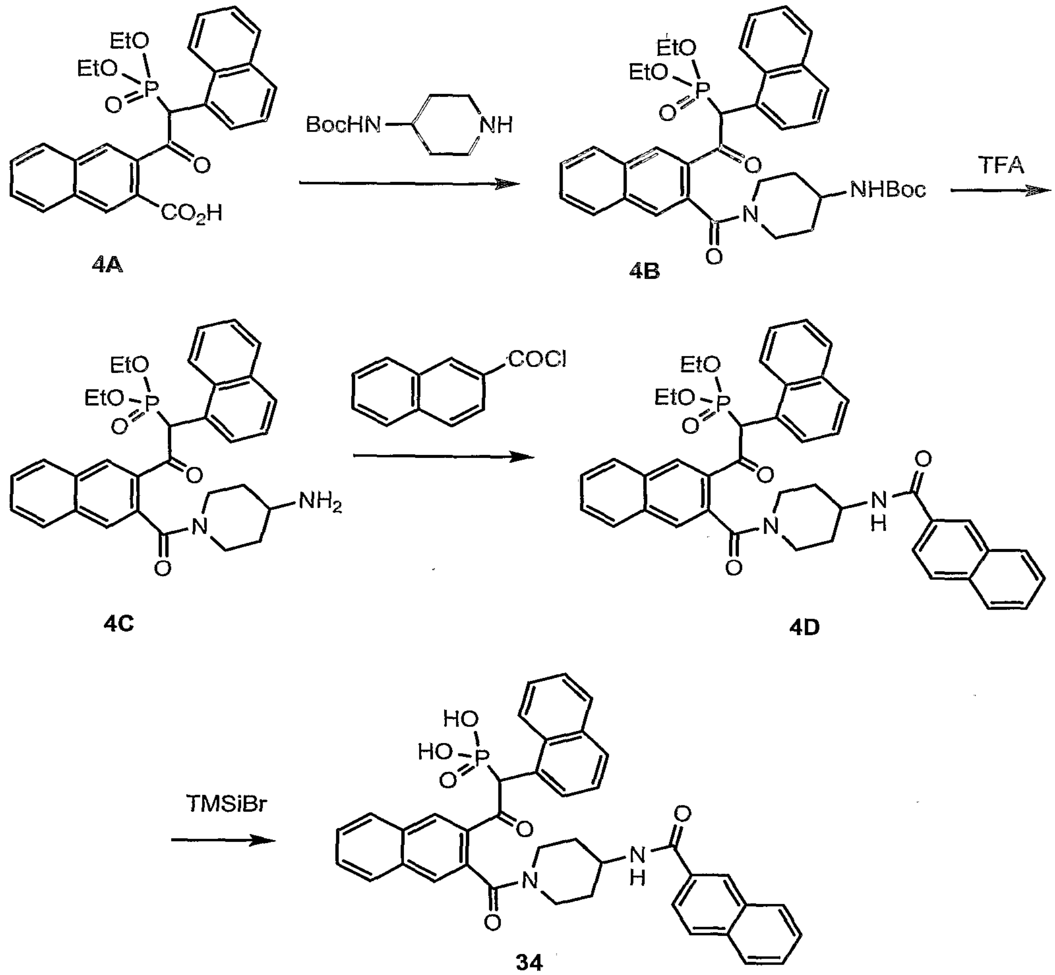
A solution of **4A** (1.0 g, 2.1 mmol), 4-*N*-Boc-aminopiperidine (0.42 g, 2.2 mmol; Astatech Inc.) and HOBt (0.28 g, 2.1 mmol) in 5 mL of DMF was treated with a solution of DCC (0.43 g, 2.1 mmol) in 1 mL of DMF dropwise. After stirring for 24 h, the mixture was filtered through dicalite and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (silica; 5% CH_3OH-CH_2Cl_2) to afford 1 g of **4B** as a white foam, 72%. MS (ES) m/z 731 (MH^+ adduct ion with MeOH and CH_3CN).

A solution of 20% TFA in CH_2Cl_2 and **4B** (1 g, 1.5 mmol) was stirred for 45 min,

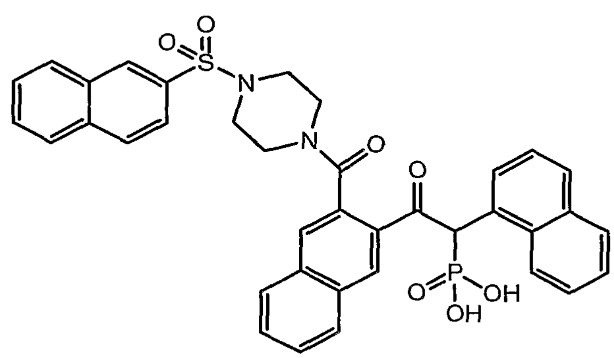
then concentrated under a stream of N_2. The residue was triturated with ether to give 0.80 g of **C** as a white powder (TFA salt): MS (ES) m/z = 530 $(M-C_2H_5)^+$.

To a mixture of 0.40 g (0.59 mmol) of **4C** and 0.17 mL (1.2 mmol) of Et_3N in 30 mL of CH_2Cl_2 was added a solution of 2-naphthoyl chloride (0.11 g, 0.60 mmol) in 1 mL of CH_2Cl_2. The reaction was stirred for 2 h, then diluted with water and the layers were separated. The organic layer was washed sequentially with H_2O, $NaHCO_3$ (satd, aq.), 1N $KHSO_4$ (aq), and H_2O, then dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (silica, 5% CH_3OH-CH_2Cl_2) to afford 0.29 g (70%) of **4D** as a white powder: MS (ES) m/z 713 (MH^+).

A solution of 0.29 g (0.40 mmol) of **4D** in 2.5 mL of pyridine was treated with 0.4 mL (3.3 mmol) of bromotrimethylsilane and the mixture was stirred for 2 h. Volatiles were removed under reduced pressure, and the white solid residue was treated with 15 mL of 1N HCl (aq). The slurry was stirred for 2.5 h and the white solid was collected and rinsed with H_2O. The solid was triturated with CH_3CN to yield 0.12 g of the title compound (46%) as a white powder: MS (ES) m/z 657 (MH^+).



Example 5

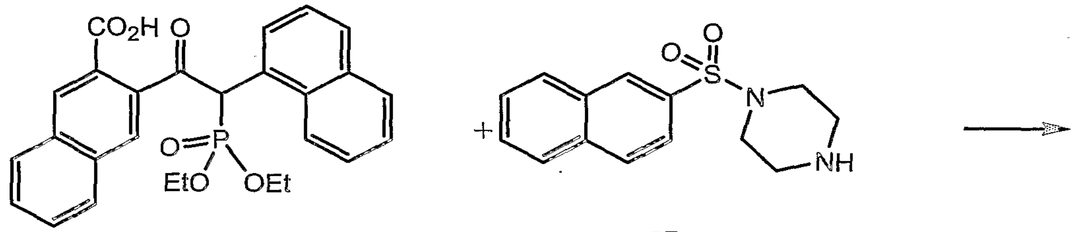


(2-{3-[4-(Naphthalene-2-sulfonyl)-piperazine-1-carbonyl]-naphthalen-2-yl}-1-naphthalen-1-yl-2-oxo-ethyl)-phosphonic acid

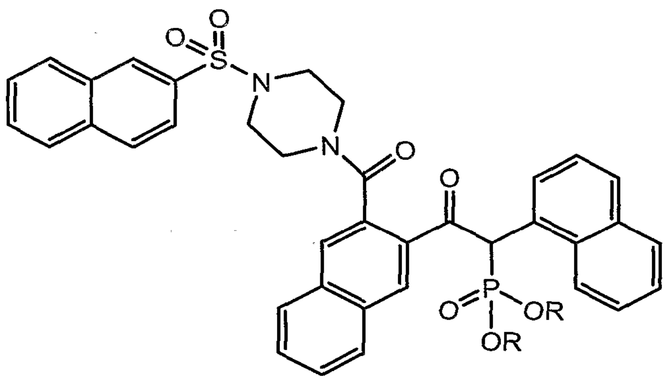
Compound 35

To a stirred solution of 5A (0.55 g, 1.16 mmol), the trifluoroacetate salt of 5B (0.5 g, 1.16 mmol), triethylamine (1.28 mmol, 0.18 mL), and HOBt (0.24 g, 1.75 mmol) in 5 mL of acetonitrile was added a solution of DCC in 2 mL of acetonitrile. (0.26 g, 1.28 mmol). The reaction was stirred for 24 h, then treated with 1 mL of DIPEA, and stirred an additional 5 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica; 100% CH_2Cl_2 -> 98% CH_2Cl_2-MeOH) to afford 0.66 g of **5C** as a foam: MS (ES^+) MH^+ = 735.

To a stirred solution of **5C** (0.11 g, 0.75 mmol) in 1 mL of pyridine was added 0.15 mL of bromotrimethylsilane. The reaction was stirred for 1.5 h, then concentrated under reduced pressure. The residue was stirred with excess 3N HCl for 1 h, and the product collected and washed sequentially with water and ether. The product was suspended in acetonitrile and stirred for 0.5 h at 0°C then collected to afford 0.067 g of the title compound as a white solid: MS (ES^+) MH^+ = 679.



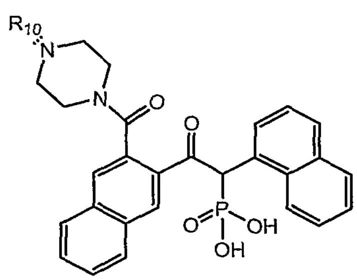
5A **5B**



5C R = Et

35 R = H

Following the procedure of Example 5 and substituting the appropriate starting materials, compounds and reagents, the following Compounds of the invention were also prepared:



Cpd	R_{10}	MS m/e (MH^+).
37	naphthalene-2-yl-acetyl	657

38	2-naphthoyl	641 (MH^-)
39	1-(4-hydroxyphenyl)	581
40	1-(4-methoxyphenyl)	595
41	N-[5-(sulfonyl)-thiophene-2-ylmethyl]-benzamide	768
42	6-chloro-5-sulfonyl-imidazo[2,1-b]thiazole	709
43	Naphthyl-2-aminocarbonyl	658
44	1-(4-fluorophenyl)	583

Biological Experimental Examples

The utility of the compounds of the present invention as a serine protease inhibitor and, particularly, as a cathepsin G or chymase inhibitor useful for the treatment of inflammatory or serine protease mediated disorders can be determined according to the procedures described herein.

Example 1

Enzyme-Catalyzed Hydrolysis Assays - Cathepsin G

Enzyme-catalyzed hydrolysis rates were measured spectrophotometrically using human neutrophil cathepsin G (Athens Research and Technology) or human skin chymase (Cortex Biochem), a chromogenic substrate (Suc-Ala-Ala-Pro-Phe-pNa) (Bachem) in aqueous buffer (100 mM Hepes, 500 mM NaCl, pH 7.4 for catG; 450 mM Tris, 1800 mM NaCl, pH 8.0 for chymase), and a microplate reader (Molecular Devices). IC_{50} experiments were conducted by fixing the enzyme and substrate concentrations (70 nM enzyme, 5 mM substrate for cat G, 10 nM enzyme, 0.7 mM substrate for chymase) and varying the inhibitor concentration. Changes in absorbance at 405 nM were monitored using the software program Softmax (Molecular Devices), upon addition of enzyme, with and without inhibitor present at 37°C for 30 minutes. Percent inhibition was calculated by comparing the initial reaction slopes of the samples without inhibitor to those with inhibitor. IC_{50} values were determined using a

four parameter fit logistics model. The term "NT" indicates a compound that was not tested.

Table 4 summarizes the assay results for cathepsin G and chymase inhibition for compounds of the present invention:

Table 4

Cpd	IC_{50} (μM) CatG	n	IC_{50} (μM) Chymase	n
1	0.083 ± 0.014	7	0.0053 ± 0.0019	8
2	0.081 ± 0.009	70	0.0067 ± 0.0018	70
3	0.068 ± 0.019	2	0.072 ± 0.008	3
4	0.090 ± 0.020	5	0.0039 ± 0.0001	4
5	0.072 ± 0.021	5	0.2 ± 0.4	6
6	0.067 ± 0.014	4	0.0035 ± 0.0015	2
7	0.210 ± 0.050	12	0.008 ± 0.022	1
8	0.130 ± 0.010	11	0.0074 ± 0.0022	8
9	0.053 ± 0.015	5	0.011 ± 0.003	2
10	0.053 ± 0.016	5	0.014 ± 0.006	5
11	4.9 ± 2.8	2	0.032	1
12	0.179 ± 0.038	10	0.0073 ± 0.0017	10
13	0.064 ± 0.008	3	0.004	1
14	0.230 ± 0.030	6	0.010 ± 0.001	9
15	0.075 ± 0.030	5	0.017 ± 0.005	3
16	0.190 ± 0.020	7	0.0085 ± 0.0023	7
17	0.098 ± 0.026	4	0.0072 ± 0.0015	6
18	0.028 ± 0.006	3	0.0010	1
19	0.238 ± 0.030	8	0.022 ± 0.062	9
20	0.090 ± 0.023	5	0.004 ± 0.002	2
21	0.070 ± 0.020	5	0.0096 ± 0.0034	5
22	0.140 ± 0.040	18	0.009 ± 0.023	12
23	0.670	1	0.416	1
24	0.078 ± 0.015	7	0.0035 ± 0.0013	6
25	0.156 ± 0.028	7	0.0097 ± 0.0035	7
26	0.096 ± 0.018	3	0.015 ± 0.001	3

Cpd	IC_{50} (μM) CatG	n	IC_{50} (μM) Chymase	n
27	0.070 ± 0.010	4	0.0051 ± 0.0022	4
28	0.400 ± 0.090	11	0.036 ± 0.011	10
29	0.150 ± 0.030	13	0.0082 ± 0.0028	10
30	0.590 ± 0.040	2	0.0158 ± 0.0008	2
31	>100.0	1	14.95 ± 0.67	2
32	0.86 ± 0.03	2	0.31	1
33	0.121 ± 0.007	2	0.001 ± 0.000	2
34	0.09 ± 0.04	3	0.007 ± 0.001	2
35	0.56 ± 0.18	3		
37	0.74 ± 0.29	3		
38	0.78 ± 0.22	2		
39	0.18 ± 0.05	2		
40	0.17 ± 0.05	2		
41	0.31	1		
42	0.14 ± 0.03	2		
43	0.95 ± 0.21	5		
44	0.52 ± 0.29	2		

Example 2

Anti-Asthmatic Effects in a Sheep Model of Asthma

The efficacy of Compound **2** for the treatment of asthma was evaluated in a validated model of *Ascaris suum* antigen-induced asthmatic response in conscious sheep (Abraham, W.M., Pharmacology of allergen-induced early and late airway responses and antigen-induced airway hyperresponsiveness in allergic sheep, *Pulmonary Pharmacology,* **1989**, 2, 33-40).

Experimental Protocol

Baseline dose response curves to aerosol carbachol were obtained 1-3 days prior to antigen challenge. Baseline values of specific lung resistance (SR_L) were obtained and the sheep were then given a specified amount (mg) of the test compound as an inhaled aerosol at a specified time before antigen challenge. Post drug measurements of SR_L were obtained and the sheep were

then challenged with *Ascaris suum* antigen. Measurements of SR_L were obtained immediately after challenge, hourly from 1-6 h after challenge and on the half-hour from 6½-8 h after challenge. Measurements of SR_L were obtained 24 h after challenge followed by a 24 h post-challenge with carbachol to measure airway hyperreactivity.

Compound **2** was administered as an aerosol at 0.1 mg/Kg/dose, twice-a-day (*BID*) for three consecutive days, followed by a dose on day 4, 0.5 h prior to antigen challenge. *Ascaris suum* antigen challenge was given at the zero time point.

Figure 1 shows that the early airway response (0-2 h after antigen challenge) was dramatically reduced and that the late airway response (6-8 h after antigen challenge) was completely blocked (n = 4 sheep/group).

Figure 2 shows that the delayed airway hyperreactivity measured at 24 h post antigen challenge as measured using carbachol challenge was also completely blocked.

In addtion to blocking the increase in airway resistance, as shown in Table 5, Compound **2** also blocked the rise in inflammatory cell numbers in the broncho-alveolar lavage (BAL) fluid sampled from these sheep.

Table 5

Treatment Group/Time	**BAL Cell Count (x1000/mL)**			
Baseline	**Neutrophils**	**Lymphocytes**	**Eosinophils**	**Macrophages**
Baseline	22.04 ±12.89	4.82 ±1.74	6.29 ±3.98	172.2 ±20.8
8h Post Antigen	24.55 ±14.08	13.39 ±5.44	61.58 ±29.87	209.3 ±44.7
24h Post Antigen	111.7 ±38.9	36.30 ±15.68	168.4 ±95.1	245.6 ±20.4

Table 5

Compound 2 (1.0 mg/kg x 4 days) (last dose - 30 min prior to antigen challenge)

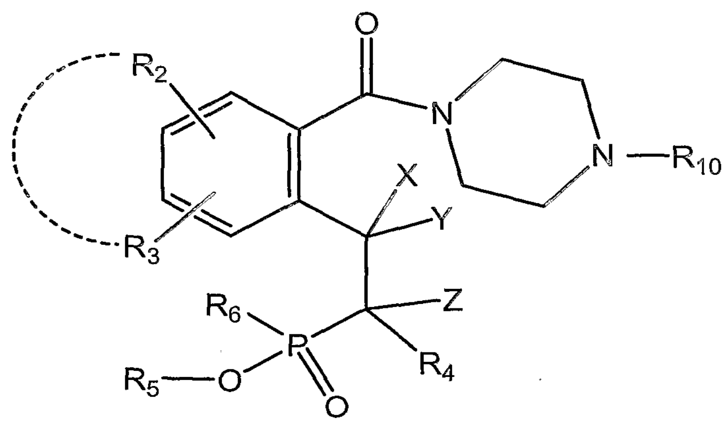
Baseline	12.66 ±2.07	3.15 ±0.79	0.00	69.06 ±1.97
8h Post Antigen	3.17 ±0.65	4.16 ±1.10	0.37 ±0.32	77.85 ±2.36
24h Post Antigen	3.86 ±0.95	3.72 ±0.77	0.04 ± 0.03	75.16 ±2.71

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

CLAIMS

What is claimed is:

1. A compounds of Formula (II):



Formula (II)

wherein

R_{10} is selected from the group consisting of:

a). sulfonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, heteroaryl(C_{1-8})alkyl and heteroaryl(C_{2-8})alkenyl;

b). carbonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl heteroaryl, heteroaryl(C_{1-8})alkyl, heteroaryl(C_{2-8})alkenyl, $-OR_{11}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, aryl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

c). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, $(halo)_{1-3}$, hydroxy, $-C(O)R_{12}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

d). aryl;
e). heteroaryl;
f). cycloalkyl
g). cycloalkenyl ; and,
h). heterocyclyl

wherein the heterocycl, cycloalkyl, cycloalkenyl portion of a)., b)., and c)., the cylcoalkyl f)., cylcoalkenyl g)., and heterocyclyl h). are optionally substituted with one to two substituents independently selected from the group consisting of:

ea). oxo
eb). carbonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl , aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl heteroaryl, heteroaryl(C_{1-8})alkyl, heteroaryl(C_{2-8})alkenyl and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);
ec). C_{1-8} alkyl optinally substituted with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl), aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, $(\text{halo})_{1-3}$, and hydroxy;
ed). aryl; and
ef). $(\text{halo})_{1-3}$

wherein the aryl portion of the a)., b)., c)., ec). and ed). substituents , the heteroaryl portion of the a)., b)., c). and ec). substituents and the d). aryl and e). heteroaryl substituents are optionally substituted with one to four substituents independently selected from the group consisting of
fa). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a

substituent selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, $(halo)_{1-3}$, hydroxy, $-C(O)R_{12}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

fb). C_{2-8} alkenyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy;

fc). C_{1-8} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

fd). cycloalkyl,

fe). heterocyclyl,

ff). aryl optionally substituted with one to four substituents independently selected from the group consisting of C_{1-8} alkyl and halogen;

fg). heteroaryl,

fh). hydroxy;

fI). nitro; and

fJ). $(halo)_{1-3}$;

wherein the aryl portion of the arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl of fa). are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy), C_{1-4} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$), amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), halogen, hydroxy and nitro;

R_{11} is selected from the group consisting of:

aa). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl portions of the aa). substituent are optionally substituted with one to four substituents independently selected from the group consisting of:

ba). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

bb). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of carboxyl, $(halo)_{1-3}$ and hydroxy;

bc). carbonyl substituted with a substituent selected from the group consisting of C_{1-4} alkyl, aryl, aryl(C_{1-4})alkyl, aryl(C_{2-4})alkenyl, heteroaryl, heteroaryl(C_{1-4})alkyl and heteroaryl(C_{2-4})alkenyl;

bd). aryl;

be). heteroaryl;

bf). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

bg). cyano;

bh). $(halo)_{1-3}$;

bi). hydroxy;

bj). nitro;

bk). heterocyclyl optionally substituted with one to two oxo substituents; and,

bl). sulfonyl substituted with a substituent selected from the group consisting of C_{1-4} alkyl, aryl, aryl(C_{1-4})alkyl, aryl(C_{2-4})alkenyl, heteroaryl, heteroaryl(C_{1-4})alkyl and heteroaryl(C_{2-4})alkenyl;

wherein the bd). aryl, be). heteroaryl and bk). heterocyclyl substituents and the aryl and heteroaryl portions of the bc). substituent are optionally substituted

with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy), C_{1-4} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$), amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), halogen, hydroxy and nitro;

R_{12} is selected from the group consisting of C_{1-4} alkyl, aryl, aryl(C_{1-4})alkyl, aryl(C_{2-4})alkenyl, cycloalkyl, cycloalkenyl, heterocycl heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryl(C_{2-4})alkenyl, $-OR_{11}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-4} alkyl, arylC_{1-4} alkyl, arylcarbonyl, arylC_{1-4} alkyl carbonyl and heteroaryl C_{1-4} alkyl);

wherein the aryl, the heteroaryl portion of R_{12} are optionally substituted with one to four substituents independently selected from the group consisting of

fa). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, $(halo)_{1-3}$, hydroxy, $-C(O)R_{11}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-4} alkyl, arylcarbonyl, arylC_{1-4} alkyl carbonyl and heteroaryl C_{1-4} alkyl);

fb). C_{2-4} alkenyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

fc). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

fd). cycloalkyl,

fe). heterocyclyl,

ff). aryl optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl and halogen;

fg). heteroaryl,

fh). halogen;

fi). hydroxy;

fj). nitro; and

fk). $(halo)_{1-3}$;

wherein the aryl portion of the arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl of fa). are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy), C_{1-4} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$), amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), halogen, hydroxy and nitro;

R_4 is selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl and heteroaryl), aryl and heteroaryl; wherein aryl and heteroaryl and the aryl and heteroaryl portions of the substituted alkyl are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cyano, halogen, hydroxy and $(halo)_{1-3}(C_{1-8})$alkyl;

R_2 and R_3 are attached to a benzene ring and independently selected from the group consisting of

ca). hydrogen;

cb). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

cc). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

cd). C_{2-4} alkenyl;

ce). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

cf). halogen; and,

cg). hydroxy;

optionally, R_2 and R_3 together form at least one ring fused to the benzene ring; thereby providing a multiple ring system; wherein the multiple ring system is selected from the group consisting of C_9-C_{14} benzo fused cycloalkyl, C_9-C_{14} benzo fused cycloalkenyl, C_9-C_{14} benzo fused aryl, benzo fused heterocyclyl and benzo fused heteroaryl; and, wherein the multiple ring system can optionally be substituted with one to four substituents independently selected from the group consisting of

da). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy;

db). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy;

dc). amino substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

dd). halogen;

de). hydroxy; and,

df). nitro;

R_5 is selected from the group consisting of hydrogen and C_{1-8} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), $(halo)_{1-3}$ and hydroxy) and aryl (optionally substituted with one to four substituents independently selected from the group consisting of C_{1-8} alkyl and halogen);

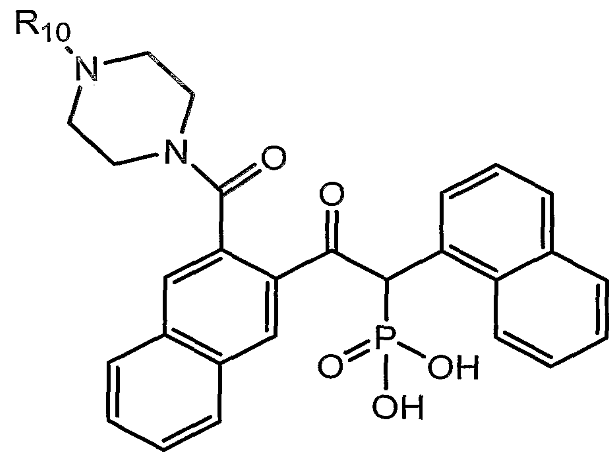
R_6 is selected from the group consisting of C_{1-8} alkyl, aryl(C_{1-8})alkyl, C_{1-8} alkoxy, aryl(C_{1-8})alkoxy, C_{2-8} alkenyl, C_{2-8} alkenyloxy, aryl(C_{2-8})alkenyl, aryl(C_{2-8})alkenyloxy, aryl, aryloxy and hydroxy;

X and Y are independently selected from the group consisting of hydrogen, C_{1-8} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(halo)_{1-3}$ and hydroxy), C_{1-8} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, $(halo)_{1-3}$ and hydroxy), C_{2-8} alkenyloxy, cycloalkyl, heterocyclyl, aryl, aryloxy, heteroaryl and hydroxy; optionally, X and Y are fused together with the carbon of attachment to form a spiro cycloalkyl or heterocyclyl moiety; and, optionally, Y is not present; wherein X is one substituent attached by a double-bond selected from the group consisting of O, S, imino, (C_{1-4})alkylimino and hydroxyimino; and,

Z is selected from the group consisting of a bond, hydrogen and C_{1-8} alkyl; if Z is a bond (wherein Z forms a double bond with the carbon of attachment for X), then Y is not present and X is one substituent attached by a single-bond selected from the group consisting of hydrogen, C_{1-8} alkoxy, C_{2-8} alkenyloxy, aryloxy, aryl(C_{1-4})alkoxy and hydroxy,

and isomers, racemates, enantiomers, diastereomers and salts thereof.

2. A compound of Formula (IIa)



Formula IIa

wherein

R_{10} is selected from the group consisting of:

a). sulfonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, heteroaryl(C_{1-8})alkyl and heteroaryl(C_{2-8})alkenyl;

b). carbonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl, aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl heteroaryl, heteroaryl(C_{1-8})alkyl, heteroaryl(C_{2-8})alkenyl, $-OR_{11}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, aryl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

c). C_{1-8} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, $(halo)_{1-3}$, hydroxy, $-C(O)R_{12}$ and amino (with two substituents independently selected from the group

consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

d). aryl;

e). heteroaryl;

f). cycloalkyl

g). cycloalkenyl ; and,

h). heterocyclyl

wherein the heterocycl, cycloalkyl, cycloalkenyl portion of a)., b)., and c)., the cylcoalkyl f)., cylcoalkenyl g)., and heterocyclyl h). are optionally substituted with one to two substituents independently selected from the group consisting of:

ea). oxo

eb). carbonyl substituted with a substituent selected from the group consisting of C_{1-8} alkyl , aryl, aryl(C_{1-8})alkyl, aryl(C_{2-8})alkenyl, cycloalkyl, cycloalkenyl, heterocycl heteroaryl, heteroaryl(C_{1-8})alkyl, heteroaryl(C_{2-8})alkenyl and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

ec). C_{1-8} alkyl optinally substituted with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl), aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, (halo)$_{1-3}$, and hydroxy;

ed). aryl; and

ef). (halo)$_{1-3}$

wherein the aryl portion of the a)., b)., c)., ec). and ed). substituents , the heteroaryl portion of the a)., b)., c). and ec). substituents and the d). aryl and e). heteroaryl substituents are optionally substituted with one to four substituents independently selected from the group consisting of

fa). C_{1-4} alkyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heterocycl, heteroaryl, $(\text{halo})_{1-3}$, hydroxy, $-C(O)R_{12}$ and amino (with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl, arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl and heteroaryl C_{1-8} alkyl);

fb). C_{2-4} alkenyl optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(\text{halo})_{1-3}$ and hydroxy;

fc). C_{1-4} alkoxy optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(\text{halo})_{1-3}$ and hydroxy;

fd). cycloalkyl,

fe). heterocyclyl,

ff). aryl optionally substituted with one to four substituents independently selected from the group consisting of C_{1-8} alkyl and halogen;

fg). heteroaryl,

fh). hydroxy;

fi). hydroxy;

fj). nitro; and

fk). $(\text{halo})_{1-3}$;

wherein the aryl portion of the arylC_{1-8} alkyl, arylcarbonyl, arylC_{1-8} alkyl carbonyl of fa). are optionally substituted with one to four substituents independently selected from the group consisting of C_{1-4} alkyl (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), $(\text{halo})_{1-3}$ and hydroxy), C_{1-4} alkoxy (optionally substituted on a terminal carbon atom with a substituent selected from the group consisting of $(\text{halo})_{1-3}$), amino (substituted with two substituents independently selected from the group consisting of hydrogen

and C_{1-4} alkyl), halogen, hydroxy and nitro.

3. The compound of claim 2 wherein R_{10} is selected from the group consisting of

2-naphthalene-sulfonyl,

naphthalene-2-yl-acetyl,

2-naphthoyl,

1-(4-hydroxyphenyl),

1-(4-methoxyphenyl),

N-[5-(sulfonyl)-thiophene-2-ylmethyl]-benzamide,

6-chloro-5-sulfonyl-imidazo[2,1-b]thiazole,

Naphthyl-2-aminocarbonyl, and

1-(4-fluorophenyl).

4. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

5. A process for preparing a composition comprising mixing the compound of claim 1 and a pharmaceutically acceptable carrier.

6. A method for treating an inflammatory or serine protease mediated disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of claim 1.

7. The method of claim 6 wherein the inflammatory or serine protease mediated disorder is selected from the group consisting of pulmonary inflammatory conditions, chronic obstructive pulmonary diseases, asthma, pulmonary emphysema, bronchitis, psoriasis, allergic rhinitis, viral rhinitis,

ischemia, arthritis, glomerulonephritis,postoperative adhesion formation, reperfusion injury, hypertension, hypercardia myocardial infraction, arteriosclerosis, retinopathy, and vascular restenosis.

8. The method of claim 7 wherein the therapeutically effective amount of the compound of claim 1 [HBW CLAIM 1 HAS BEEN DELETED) is from about 0.001 mg/kg/day to about 300 mg/kg/day.

9. The method of claim 7 further comprising administering to the subject a therapeutically effective amount of the composition of claim 5.

Fig. 1/2

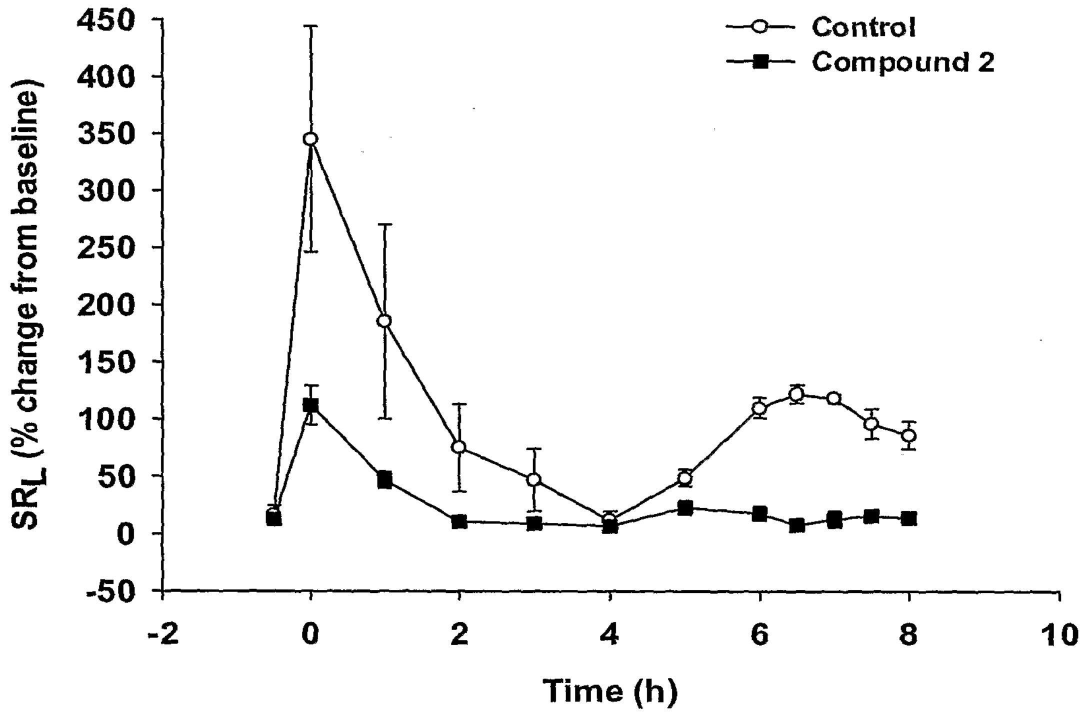
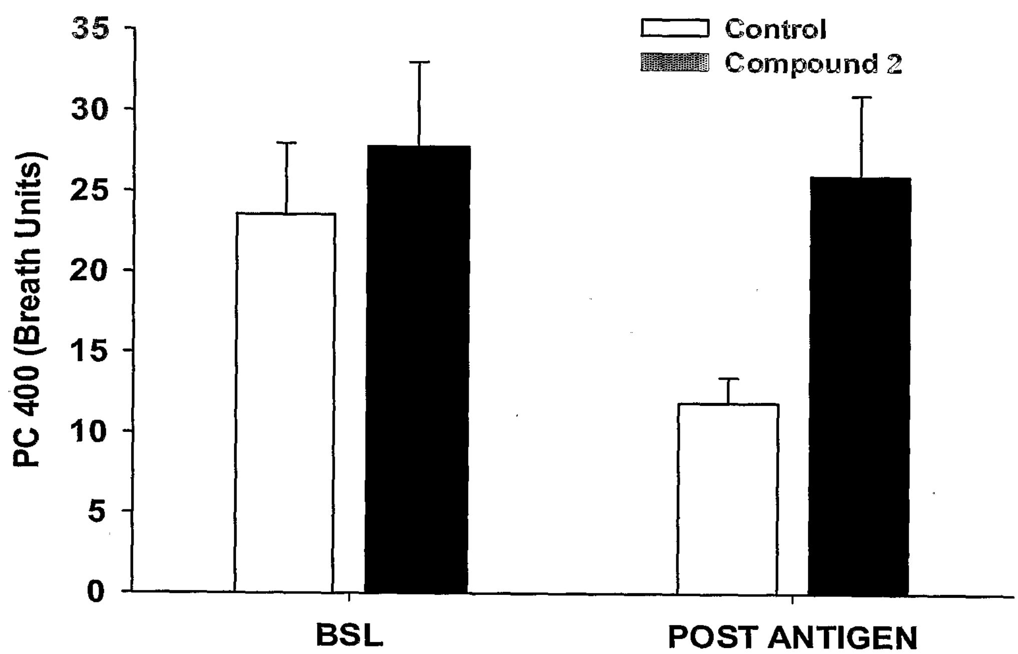

Control
Compound 2
SR_L (% change from baseline)
450
400
350
300
250
200
150
100
50
0
-50
-2
0
2
4
6
8
10
Time (h)

Fig. 2/2


35
30
25
20
15
10
5
0
PC 400 (Breath Units)
Control
Compound 2
BSL
POST ANTIGEN

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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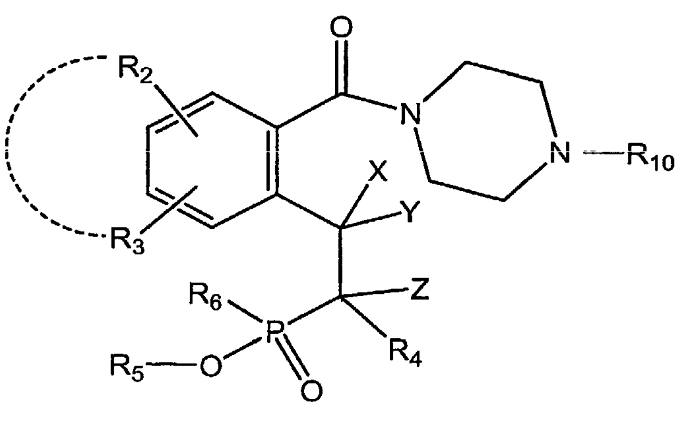
Published:
— *with international search report*

(88) Date of publication of the international search report: 13 October 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PIPERAZINE CONTAINING PHOSPHONIC ACID COMPOUNDS AS INHIBITORS OF SERINE PROTEASES



(II)

(57) Abstract: The present invention is directed to phosphonic acid compounds of Formula (II): useful as serine protease inhibitors, compositions thereof and methods for treating inflammatory and serine protease mediated disorders.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/011490

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F9/6509 C07F9/6558 C07F9/6561 A61K31/675 C07F9/572
C07F9/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 704 382 A (FOWLER KERRY W ET AL) 3 November 1987 (1987-11-03) column 1, line 23 - line 31 table 1, compound 11	1-9
P,A	WO 03/035654 A (ORTHO MCNEIL PHARM INC) 1 May 2003 (2003-05-01) page 26, table 2, compounds 7,12,14,16 page 35, line 8 - line 21 claims 25,28,30	1-9
A	US 4 822 780 A (TSUDA YOSHIAKI ET AL) 18 April 1989 (1989-04-18) column 1, line 27 - line 38 column 4, line 4 - line 28 claims 1,6	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention *cannot be considered novel or cannot be considered* to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2004	07/01/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	O'Sullivan, P

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/011490

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 6-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/011490

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